

# WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5: C12N 15/51, C12Q 1/68, A61K 39/29, G01N 33/576, C07N 14/18, C12Q 1/70, C07K 16/10

(11) International Publication Number: **A2** 

WO 94/25601

(43) International Publication Date: 10 November 1994 (10.11.94)

(21) International Application Number:

PCT/EP94/01323

(22) International Filing Date:

27 April 1994 (27.04.94)

(30) Priority Data:

93401099.2 27 April 1993 (27.04.93) EP (34) Countries for which the regional or international application was filed: GB et al. 93402019.9 5 August 1993 (05.08.93) EP

(34) Countries for which the regional or international application was filed:

GB et al.

(71) Applicant (for all designated States except US): N.V. INNO-GENETICS S.A. [BE/BE]; Industriepark, Zwihnaarde 7, Box 4, B-9052 Ghent (BE).

(72) Inventors: and

(75) Inventors/Applicants (for US only): MAERTENS, Geert [BE/BE]; Zilversparrenstrasse 64, B-8310 Brugge (BE). STUYVER, Lieven [BE/BE]; Hoogstraat 27, B-9340 Lede (BE).

(74) Agent: GROSSET-FOURNIER, Chantal; Grosset-Fournier & Demachy S.A.R.L., 103, rue La Fayette, F-75010 Paris (FR). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT. RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

#### **Published**

Without international search report and to be republished upon receipt of that report.

(54) Title: NEW SEQUENCES OF HEPATITIS C VIRUS GENOTYPES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC **AGENTS** 

#### (57) Abstract

The present invention relates to a polynucleic acid composition comprising or consisting of at least one polynucleic acid containing 8 or more contiguous nucleotides corresponding to a nucleotide sequence from the region spanning positions 417 to 957 of the Core/E1 region of HCV type 3; and/or the region spanning positions 4664 to 4730 of the NS3 region of HCV type 3; and/or the region spanning positions 4892 to 5292 of the NS3/4 region of HCV type 3; and/or the region spanning positions 8 023 to 8 235 of the NS5 region of the BR36 subgroup of HCV type 3a; and/or the coding region of HCV type 4a starting at nucleotide 379 in the core region; and/or the coding region of HCV type 4; and/or the coding region of HCV type 5, with said nucleotide numbering being with respect to the numbering of HCV nucleic acids as shown in Table 1, and with said polynucleic acids containing at least one nucleotide difference with known HCV type 1, and/or HCV type 2 genomes in the above-indicated regions, or the complement thereof.



### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Materitania
ΑÜ	Australia	GR	Georgia		
BB	Barbados	GN	Guinea	MW	Malawi
BE	Belgium	GR	Greece	NB	Niger
BF	Burkina Feso	HU	Hungary	NL	Netherlands
BG	Bulgaria	DE.	Ireland	NO	Norway
BJ	Benin	ΪŢ		NZ	New Zealand
BR	Brazil		Italy	PL.	Poland
BY	<del></del>	JР	Japan	PT	Portugal
_	Belarus	KR	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF.	Central African Republic	KP	Democratic People's Republic	SD	Sudan
CG	, Congo		of Korea	SR	Sweden
CE	Switzerland	KR	Republic of Korea	SI	Slovenia
α	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	Ц	Liechtenstein	SN	Scorgal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tailkistan
DE	Germany	MC	Monaco	II	•
DK	Denmark	MD	Republic of Moldova		Trinidad and Tobago
ES	Spain	MG	Madagascar	- UA	Ukraine
FI	Pinland	MIL	<b>-</b>	US	United States of America
FR	Prance		Mali	UZ	Uzbekistan
GA	Gabon	MN	Mongolia	VN	Vict Nam
UA.					

1

NEW SEQUENCES OF HEPATITIS C VIRUS GENOTYPES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC AGENTS

The invention relates to new sequences of hepatitis C virus (HCV) genotypes and their use as therapeutic and diagnostic agents.

The present invention relates to new nucleotide and amino acid sequences corresponding to the coding region of a new type 2 subtype 2d, type-specific sequences corresponding to HCV type 3a, to new sequences corresponding to the coding region of a new subtype 3c, and to new sequences corresponding to the coding region of HCV type 4 and type 5 subtype 5a; a process for preparing them, and their use for diagnosis, prophylaxis and therapy.

The technical problem underlying the present invention is to provide new type-specific sequences of the Core, the E1, the E2, the NS3, the NS4 and the NS5 regions of HCV type 4 and type 5, as well as of new variants of HCV types 2 and 3. These new HCV sequences are useful to diagnose the presence of type 2 and/or type 3 and/or type 4 and/or type 5 HCV genotypes in a biological sample. Moreover, the availability of these new type-specific sequences can increase the overall sensitivity of HCV detection and should also prove to be useful for therapeutic purposes.

Hepatitis C viruses (HCV) have been found to be the major cause of non-A, non-B hepatitis. The sequences of cDNA clones covering the complete genome of several prototype isolates have been determined (Kato et al., 1990; Choo et al., 1991; Okamoto et al., 1991; Okamoto et al., 1992). Comparison of these isolates shows that the variability in nucleotide sequences can be used to distinguish at least 2 different genotypes, type 1 (HCV-1 and HCV-J) and type 2 (HC-J6 and HC-J8), with an average homology of about 68%. Within each type, at least two subtypes exist (e.g. represented by HCV-1 and HCV-J), having an average homology of about 79%. HCV genomes belonging to the same subtype show average homologies of more than 90% (Okamoto et al., 1992). However, the partial nucleotide sequence of the NS5 region of the HCV-T isolates showed at most 67% homology with the previously published sequences, indicating the existence of a yet another HCV type (Mori et al., 1992). Parts of the 5' untranslated region (UR), core, NS3, and NS5 regions of this type 3 have been published, further establishing the similar evolutionary distances between the 3 major genotypes and their subtypes (Chan et al., 1992).

The identification of type 3 genotypes in clinical samples can be achieved by means of PCR with type-specific primers for the NS5 region. However, the degree to which this will

be successful is largely dependent on sequence variability and on the virus titer present in the serum. Therefore, routine PCR in the open reading frame, especially for type 3 and the new type 4 and 5 described in the present invention and/or group V (Cha et al., 1992) genotypes can be predicted to be unsuccessful. A new typing system (LiPA), based on variation in the highly conserved 5' UR, proved to be more useful because the 5 major HCV genotypes and their subtypes can be determined (Stuyver et al., 1993). The selection of high-titer isolates enables to obtain PCR fragments for cloning with only 2 primers, while nested PCR requires that 4 primers match the unknown sequences of the new type 3, 4 and 5 genotypes.

New sequences of the 5' untranslated region (5'UR) have been listed by Bukh et al. (1992). For some of these, the E1 region has recently been described (Bukh et al., 1993). Isolates with similar sequences in the 5'UR to a group of isolates including DK12 and HK10 described by Bukh et al. (1992) and E-b1 to E-b8 described and classified as type 3 by Chan et al. (1991), have been reported and described in the 5'UR, the carboxyterminal part of E1, and in the NS5 region as group IV by Cha et al. (1992; WO 92/19743), and have also been described in the 5'UR for isolate BR56 and classified as type 3 by the inventors of this application (Stuyver et al., 1993).

The aim of the present invention is to provide new HCV nucleotide and amino acid sequences enabling the detection of HCV infection.

Another aim of the present infection is to provide new nucleotide and amino acid HCV sequences enabling the classification of infected biological fluids into different serological groups unambiguously linked to types and subtypes at the genome level.

Another aim of the present invention is to provide new nucleotide and amino acid HCV sequences ameliorating the overall HCV detection rate.

Another aim of the present invention is to provide new HCV sequences, useful for the design of HCV vaccine compositions.

Another aim of the present invention is to provide a pharmaceutical composition consisting of antibodies raised against the polypeptides encoded by these new HCV sequences, for therapy or diagnosis.

The present invention relates more particularly to a composition comprising or consisting of at least one polynucleic acid containing at least 5, and preferably 8 or more contiguous nucleotides selected from at least one of the following HCV sequences:

- an HCV type 3 genomic sequence, more particularly in any of the following regions:

- the region spanning positions 417 to 957 of the Core/E1 region of HCV subtype 3a,
- the region spanning positions 4664 to 4730 of the NS3 region of HCV type 3,
- the region spanning positions 4892 to 5292 of the NS3/4 region of HCV type 3,
- the region spanning positions 8023 to 8235 of the NS5 region of the BR36 subgroup of HCV subtype 3a,
- an HCV subtype 3c genomic sequence,

more particularly the coding regions of the above-specified regions;

- an HCV subtype 2d genomic sequence, more particularly the coding region of HCV subtype 2d;
- an HCV type 4 genomic sequence, more particularly the coding region, more particularly the coding region of subtypes 4a, 4e, 4f, 4g, 4h, 4i, and 4j,
- an HCV type 5 genomic sequence, more particularly the coding region of HCV type 5, more particularly the regions encoding Core, E1, E2, NS3, and NS4

with said nucleotide numbering being with respect to the numbering of HCV nucleic acids as shown in Table 1, and with said polynucleic acids containing at least one nucleotide difference with known HCV (type 1, type 2, and type 3) polynucleic acid sequences in the above-indicated regions, or the complement thereof.

It is to be noted that the nucleotide difference in the polynucleic acids of the invention may involve or not an amino acid difference in the corresponding amino acid sequences coded by said polynucleic acids.

According to a preferred embodiment, the present invention relates to a composition comprising or containing at least one polynucleic acid encoding an HCV polyprotein, with said polynucleic acid containing at least 5, preferably at least 8 nucleotides corresponding to at least part of an HCV nucleotide sequence encoding an HCV polyprotein, and with said HCV polyprotein containing in its sequence at least one of the following amino acid residues: L7, Q43, M44, S60, R67, Q70, T71, A79, A87, N106, K115, A127, A190, S130, V134, G142, I144, E152, A157, V158, P165, S177 or Y177, I178, V180 or E180 or F182, R184, I186, H187, T189, A190, S191 or G191, Q192 or L192 or I192 or V192 or E192, N193 or H193 or P193, W194 or Y194, H195, A197 or I197 or V197 or T197, V202, I203 or L203, Q208, A210, V212, F214, T216, R217 or D217 or E217 or V217, H218 or N218, H219 or

V219 or L219, L227 or I227, M231 or E231 or Q231, T232 or D232 or A232 or K232, Q235 or I235, A237 or T237, I242, I246, S247, S248, V249, S250 or Y250, I251 or V251 or M251 or F251, D252, T254 or V254, L255 or V255, E256 or A256, M258 or F258 or V258, A260 or Q260 or S260, A261, T264 or Y264, M265, I266 or A266, A267, G268 or T268, F271 or M271 or V271, I277, M280 or H280, I284 or A284 or L84, V274, V291, N292 or S292, R293 or I293 or Y293, Q294 or R294, L297 or I297 or Q297, A299 or K299 or Q299, N303 or T303, T308 or L308, T310 or F310 or A310 or D310 or V310, L313, G317 or Q317, L333, S351, A358, A359, A363, S364, A366, T369, L373, F376, Q386, I387, S392, I399, F402, I403, R405, D454, A461, A463, T464, K484, Q500, E501, S521, K522, H524, N528, S531, S532, V534, F536, F537, M539, I546, C1282, A1283, H1310, V1312, Q1321, P1368, V1372, V1373, K1405, Q1406, S1409, A1424, A1429, C1435, S1436, S1456, H1496, A1504, D1510, D1529, I1543, N1567, D1556, N1567, M1572, Q1579, L1581, S1583, F1585, V1595, E1606 or T1606, M1611, V1612 or L1612, P1630, C1636, P1651, T1656 or I1656, L1663, V1667, V1677, A1681, H1685, E1687, G1689, V1695, A1700, Q1704, Y1705, A1713, A1714 or S1714, M1718, D1719, A1721 or T1721, R1722, A1723 or V1723, H1726 or G1726, E1730, V1732, F1735, I1736, S1737, R1738, T1739, G1740, Q1741, K1742, Q1743, A1744, T1745, L1746, E1747 or K1747, I1749, A1750, T1751 or A1751, V1753, N1755, K1756, A1757, P1758, A1759, H1762, T1763, Y1764, P2645, A2647, K2650, K2653 or L2653, S2664, N2673, F2680, K2681, L2686, H2692, Q2695 or L2695 or I2695, V2712, F2715, V2719 or Q2719, T2722, T2724, S2725, R2726, G2729, Y2735, H2739, I2748, G2746 or I2746, I2748, P2752 or K2752, P2754 or T2754, T2757 or P2757, with said notation being composed of a letter representing the amino acid residue by its one-letter code, and a number representing the amino acid numbering according to Kato et al., 1990.

Each of the above-mentioned residues can be found in any of Figures 2, 5, 7, 11 or 12 showing the new amino acid sequences of the present invention aligned with known sequences of other types or subtypes of HCV for the Core, E1, E2, NS3, NS4, and NS5 regions.

More particularly, a polynucleic acid contained in the composition according to the present invention contains at least 5, preferably 8, or more contiguous nucleotides corresponding to a sequence of contiguous nucleotides selected from at least one of HCV sequences encoding the following new HCV amino acid sequences:

- new sequences spanning amino acid positions 1 to 319 of the Core/E1 region of HCV subtype 2d, type 3 (more particularly new sequences for subtypes 3a and 3c), new type 4

subtypes (more particularly new sequences for subtypes 4a, 4e, 4f, 4g, 4h, 4i and 4j) and type 5a, as shown in Figure 5;

- new sequences spanning amino acid positions 328 to 546 of the E1/E2 region of HCV subtype 5a as shown in Figure 12;
- new sequences spanning amino acid positions 1556 to 1764 of the NS3/NS4 region of HCV type 3 (more particularly for new subtypes 3a sequences), and subtype 5a, as shown in Figure 7 or 11;
- new sequences spanning amino acid positions 2645 to 2757 of the NS5B region of HCV subtype 2d, type 3 (more particularly for new subtypes 3a and 3c), new type 4 subtypes (more particularly subtypes 4a, 4e, 4f, 4g, 4h, 4i and 4j) and subtype 5a, as shown in Figure 2,

Using the LiPA system mentioned above, Brazilian blood donors with high titer type 3 hepatitis C virus, Gabonese patients with high-titer type 4 hepatitis C virus, and a Belgian patient with high-titer HCV type 5 infection were selected. Nucleotide sequences in the core, E1, NS5 and NS4 regions which have not yet been reported before, were analyzed in the frame of the invention. Coding sequences (with the exception of the core region) of any type 4 isolate are reported for the first time in the present invention. The NS5b region was also analyzed for the new type 3 isolates. After having determined the NS5b sequences, comparison with the Ta and Tb subtypes described by Mori et al. (1992) was possible, and the type 3 sequences could be identified as type 3a genotypes. The new type 4 isolates segregated into 10 subtypes, based on homologies obtained in the NS5 and E1 regions. New type 2 and 3 sequences could also be distinguished from previously described type 2 or 3 subtypes from sera collected in Belgium and the Netherlands.

The term "polynucleic acid" refers to a single stranded or double stranded nucleic acid sequence which may contain at least 5 contiguous nucleotides to the complete nucleotide sequence (f.i. at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous nucleotides). A polynucleic acid which is up till about 100 nucleotides in length is often also referred to as an oligonucleotide. A polynucleic acid may consist of deoxyribonucleotides or ribonucleotides, nucleotide analogues or modified nucleotides, or may have been adapted for therapeutic purposes. A polynucleic acid may also comprise a double stranded cDNA clone which can be used for cloning purposes, or for *in vivo* therapy, or prophylaxis.

The term "polynucleic acid composition" refers to any kind of composition comprising essentially said polynucleic acids. Said composition may be of a diagnostic or a therapeutic

nature.

The expression "nucleotides corresponding to" refers to nucleotides which are homologous or complementary to an indicated nucleotide sequence or region within a specific HCV sequence.

The term "coding region" corresponds to the region of the HCV genome that encodes the HCV polyprotein. In fact, it comprises the complete genome with the exception of the 5' untranslated region and 3' untranslated region.

The term "HCV polyprotein" refers to the HCV polyprotein of the HCV-J isolate (Kato et al., 1990). The adenine residue at position 330 (Kato et al., 1990) is the first residue of the ATG codon that initiates the long HCV polyprotein of 3010 amino acids in HCV-J and other type 1b isolates, and of 3011 amino acids in HCV-1 and other type 1a isolates, and of 3033 amino acids in type 2 isolates HC-J6 and HC-J8 (Okamoto et al., 1992).

This adenine is designated as position 1 at the nucleic acid level, and this methionine is designated as position 1 at the amino acid level, in the present invention. As type 1a isolates contain 1 extra amino acid in the NS5a region, coding sequences of type 1a and 1b have identical numbering in the Core, E1, NS3, and NS4 region, but will differ in the NS5b region as indicated in Table 1. Type 2 isolates have 4 extra amino acids in the E2 region, and 17 or 18 extra amino acids in

the NS5 region compared to type 1 isolates, and will differ in numbering from type 1 isolates in the NS3/4 region and NS5b regions as indicated in Table 1.

### TABLE 1

	Region	Positions described in the present invention*	Positions described for HCV-J (Kato et al., 1990)	Positions described for HCV-1 (Choo et al., 1991)	Positions described for HC-J6, HC-J8 (Okamoto et al., 1992)
Nucleotide s	NS5b	8023/8235 7932/8271	8352/8564 8261/8600	8026/8238 7935/8274	8433/8645 8342/8681
·	NS3/4	4664/5292 4664/4730 4892/5292 3856/4209 4936/5292	4993/5621 4993/5059 5221/5621 4185/4528 5265/5621	4664/5292 4664/4730 4892/5292 3856/4209 4936/5292	5017/5645 5017/5083 5245/5645 4209/4762 5289/5645
		coding region of present invention	330/9359	1/9033	342/9439
Amino Acids	NS5b	2675/2745 2645/2757	2675/2745 2645/2757	2676/2746 2646/2758	2698/2768 2668/2780
	NS3/4	1556/1764 1286/1403 1646/1764	1556/1764 1286/1403 1646/1764	1556/1764 1286/1403 1646/1764	1560/1768 1290/1407 1650/1768

Table 1: Comparison of the HCV nucleotide and amino acid numbering system used in the present invention (\*) with the numbering used for other prototype isolates. For example, 8352/8564 indicates the region designated by the numbering from nucleotide 8352 to nucleotide 8564 as described by Kato et al. (1990). Since the numbering system of the present invention starts at the polyprotein initiation site, the 329 nucleotides of the 5' untranslated region described by Kato et al. (1990) have to be substracted, and the corresponding region is numbered from nucleotide 8023 ("8352-329") to 8235 ("8564-329").

The term "HCV type" corresponds to a group of HCV isolates of which the complete genome shows more than 74% homology at the nucleic acid level, or of which the NS5 region between nucleotide positions 7932 and 8271 shows more than 74% homology at the nucleic acid level, or of which the complete HCV polyprotein shows more than 78% homology at the amino acid level, or of which the NS5 region between amino acids at positions 2645 and 2757 shows more than 80% homology at the amino acid level, to polyproteins of the other isolates of the group, with said numbering beginning at the first ATG codon or first methionine of the long HCV polyprotein of the HCV-J isolate (Kato et al., 1990). Isolates belonging to different types of HCV exhibit homologies, over the complete genome, of less than 74% at the nucleic acid level and less than 78% at the amino acid level. Isolates belonging to the same type usually show homologies of about 92 to 95% at the nucleic acid level and 95 to 96% at the amino acid level when belonging to the same subtype, and those belonging to the same type but different subtypes preferably show homologies of about 79% at the nucleic acid level and 85-86% at the amino acid level.

More preferably the definition of HCV types is concluded from the classification of HCV isolates according to their nucleotide distances calculated as detailed below:

- (1) based on phylogenetic analysis of nucleic acid sequences in the NS5b region between nucleotides 7935 and 8274 (Choo et al., 1991) or 8261 and 8600 (Kato et al., 1990) or 8342 and 8681 (Okamoto et al., 1991), isolates belonging to the same HCV type show nucleotide distances of less than 0.34, usually less than 0.33, and more usually of less than 0.32, and isolates belonging to the same subtype show nucleotide distances of less than 0.135, usually of less than 0.13, and more usually of less than 0.125, and consequently isolates belonging to the same type but different subtypes show nucleotide distances ranging from 0.135 to 0.34, usually ranging from 0.1384 to 0.2477, and more usually ranging from 0.15 to 0.32, and isolates belonging to different HCV types show nucleotide distances greater than 0.34, usually greater that 0.35, and more usually of greater than 0.358, more usually ranging from 0.1384 to 0.2977.
- (2) based on phylogenetic analysis of nucleic acid sequences in the core/E1 region between nucleotides 378 and 957, isolates belonging to the same HCV type show nucleotide distances of less than 0.38, usually of less than 0.37, and more usually of less than 0.364, and isolates belonging to the same subtype show nucleotide distances of less than 0.17, usually of less than 0.16, and more usually of less than 0.15, more usually less than 0.135, more usually less than 0.134, and consequently isolates belonging to the same type but different subtypes show

nucleotide distances ranging from 0.15 to 0.38, usually ranging from 0.16 to 0.37, and more usually ranging from 0.17 to 0.36, more usually ranging from 0.133 to 0.379, and isolates belonging to different HCV types show nucleotide distances greater than 0.34, 0.35, 0.36, usually more than 0.365, and more usually of greater than 0.37.

(3) based on phylogenetic analysis of nucleic acid sequences in the NS3/NS4 region between nucleotides 4664 and 5292 (Choo et al., 1991) or between nucleotides 4993 and 5621 (Kato et al., 1990) or between nucleotides 5017 and 5645 (Okamoto et al., 1991), isolates belonging to the same HCV type show nucleotide distances of less than 0.35, usually of less than 0.34, and more usually of less than 0.33, and isolates belonging to the same subtype show nucleotide distances of less than 0.19, usually of less than 0.18, and more usually of less than 0.17, and consequently isolates belonging to the same type but different subtypes show nucleotide distances ranging from 0.17 to 0.35, usually ranging from 0.18 to 0.34, and more usually ranging from 0.19 to 0.33, and isolates belonging to different HCV types show nucleotide distances greater than 0.33, usually greater than 0.34, and more usually of greater than 0.35.

Table 2: Molecular evolutionary distances

Region	Core/E1	E1	NS5B	NS5B
	579 bp	384 bp	340 bp	222 bp
Isolates*	0.0017 - 0.1347	0.0026 - 0.2031	0.0003 - 0.1151	0.000 - 0.1323
	(0.0750 <u>+</u> 0.0245)	(0.0969 <u>+</u> 0.0289)	(0.0637 <u>+</u> 0.0229)	(0.0607 <u>+</u> 0.0205)
Subtypes*	0.1330 - 0.3794	0.1645 - 0.4869	0.1384 - 0.2977	0.117 - 0.3538
	(0.2786 <u>+</u> 0.0363)	(0.3761 <u>+</u> 0.0433)	(0.2219 <u>+</u> 0.0341)	(0.2391 <u>+</u> 0.0399)
Types*	0.3479 - 0.6306	0.4309 - 0.9561	0.3581 - 0.6670	0.3457 - 0.7471
	(0.4703 ± 0.0525)	(0.6308 <u>+</u> 0.0928)	(0.4994 <u>+</u> 0.0495)	(0.5295 <u>+</u> 0.0627)

Figures created by the PHYLIP program DNADIST are expressed as minimum to maximum (average ± standard deviation). Phylogenetic distances for isolates belonging to the same subtype ('isolates'), to different subtypes of the same type ('subtypes'), and to different types ('types') are given.

In a comparative phylogenetic analysis of available sequences, ranges of molecular evolutionary distances for different regions of the genome were calculated, based on 19,781

pairwise comparisons by means of the DNA DIST program of the phylogeny inference package PHYLIP version 3.5C (Felsenstein, 1993). The results are shown in Table 2 and indicate that although the majority of distances obtained in each region fit with classification of a certain isolate, only the ranges obtained in the 340bp NS5B-region are non-overlapping and therefor conclusive. However, as was performed in the present invention, it is preferable to obtain sequence information from at least 2 regions before final classification of a given isolate.

Designation of a number to the different types of HCV and HCV types nomenclature is based on chronological discovery of the different types. The numbering system used in the present invention might still fluctuate according to international conventions or guidelines. For example, "type 4" might be changed into "type 5" or "type 6".

The term "subtype" corresponds to a group of HCV isolates of which the complete polyprotein shows a homology of more than 90% both at the nucleic acid and amino acid levels, or of which the NS5 region between nucleotide positions 7932 and 8271 shows a homology of more than 90% at the nucleic acid level to the corresponding parts of the genomes of the other isolates of the same group, with said numbering beginning with the adenine residue of the initiation codon of the HCV polyprotein. Isolates belonging to the same type but different subtypes of HCV show homologies of more than 74% at the nucleic acid level and of more than 78% at the amino acid level.

The term "BR36 subgroup" refers to a group of type 3a HCV isolates (BR36, BR33, BR34) that are 95 %, preferably 95.5 %, most preferably 96 % homologous to the sequences as represented in SEQ ID NO 1, 3, 5, 7, 9, 11 in the NS5b region from position 8023 to 8235.

It is to be understood that extremely variable regions like the E1, E2 and NS4 regions will exhibit lower homologies than the average homology of the complete genome of the polyprotein.

Using these criteria, HCV isolates can be classified into at least 6 types. Several subtypes can clearly be distinguished in types 1, 2, 3 and 4: 1a, 1b, 2a, 2b, 2c, 2d, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i and 4j based on homologies of the 5' UR and coding regions including the part of NS5 between positions 7932 and 8271. An overview of most of the reported isolates and their proposed classification according to the typing system of the present invention as well as other proposed classifications is presented in Table 3.

Table 3

## **HCV CLASSIFICATION**

	OKA- MOTO	MORI	NAKA O	СНА	PROTOTYPE
1a	I	I	Pt	GI	HCV-1, HCV-H, HC-J1
1b	п	П	KI	GII	HCV-J, HCV-BK, HCV-T, HC-JK1, HC-J4, HCV-CHINA
1c					HC-G9
2a	ш	Ш	K2a	GIII	HC-J6
2b	IV	IV	K2b	GIII	HC-J8
2c					\$83, ARG6, ARG8, I10, T983
<b>2d</b>				•	NE92
- 3a	v	v	К3	GIV	E-b1, Ta, BR36, BR33, HD10, NZL1
3b		VI	К3	GIV	HCV-TR, Tb
3c					BE98
4a	-				Z4, GB809-4
4b					- Z1
<b>4c</b>					GB116, GB358, GB215, Z6, Z7
4d '					DK13
4e			•		GB809-2, CAM600, CAM736
4f					CAM622, CAM627
4g					GB549
4h		-			GB438
4i					CAR4/1205
4j					CAR1/501
4k					EG29
5a	•			GV .	SA3, SA4, SA1, SA7, SA11, BE95
6a					HK1, HK2, HK3, HK4

The term "complement" refers to a nucleotide sequence which is complementary to an indicated sequence and which is able to hybridize to the indicated sequences.

The composition of the invention can comprise many combinations. By way of example, the composition of the invention can comprise:

- two (or more) nucleic acids from the same region or,
- two nucleic acids (or more), respectively from different regions, for the same isolate or for different isolates,
- or nucleic acids from the same regions and from at least two different regions (for the same isolate or for different isolates).

The present invention relates more particularly to a polynucleic acid composition as defined above, wherein said polynucleic acid corresponds to a nucleotide sequence selected from any of the following HCV type 3 genomic sequences:

- an HCV genomic sequence having a homology of at least 67%, preferably more than 69%, more preferably 71%, even more preferably more than 73%, or most preferably more than 76% to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 (HD10, BR36 or BR33 sequences) in the region spanning positions 417 to 957 of the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence having a homology of at least 65%, preferably more than 67%, preferably more than 69%, even preferably more than 70%, most preferably more than 74% to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 (HD10, BR36 or BR33 sequences) in the region spanning positions 574 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence as having a homology of at least 79%, more preferably at least 81%, most preferably more than 83% or more to any of the sequences as represented in SEQ ID NO 147 (representing positions 1 to 346 of the Core region of HVC type 3c, sequence BE98) in the region spanning positions 1 to 378 of the Core region as shown in Figure 3;
- an HCV genomic sequence of HVC type 3a having a homology of at least 74%, more preferably at least 76%, most preferably more than 78% or more to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 (HD10, BR36 or BR33 sequences) in the region spanning positions 417 to 957 in the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence of HCV type 3a as having a homology of at least 74%,

preferably more than 76%, most preferably 78% or more to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 (HD10, BR36 or BR33 sequences) in the region spanning positions 574 to 957 in the E1 region as shown in Figure 4;

- an HCV genomic sequence as having a homology of more than 73.5%, preferably more than 74%, most preferably 75% homology to the sequence as represented in SEQ ID NO 29 (HCCl53 sequence) in the region spanning positions 4664 to 4730 of the NS3 region as shown in figure 6;
- an HCV genomic sequence having a homology of more than 70%, preferably more than 72%, most preferably more than 74% homology to any of the sequences as represented in SEQ ID NO 29, 31, 33, 35, 37 or 39 (HCCl53, HD10, BR36 sequences) in the region spanning positions 4892 to 5292 in the NS3/NS4 region as shown in Figure 6 or 10;
- an HCV genomic sequence of the BR36 subgroup of HCV type 3a as having a homology of more than 95%, preferably 95,5%, most preferably 96% homology to any of the sequences as represented in SEQ ID NO 5, 7, 1, 3, 9 or 11 (BR34, BR33, BR36 sequences) in the region spanning positions 8023 to 8235 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence of the BR36 subgroup of HCV type 3a as having a homology of more than 96%, preferably 96.5%, most preferably 97% homology to any of the sequences as represented in SEQ ID NO 5, 7, 1, 3, 9 or 11 (BR34, BR33, BR36 sequences) in the region spanning positions 8023 to 8192 of the NS5B region as shown in Figure 1;
- an HCV genomic sequence of HCV type 3c being characterized as having a homology of more than 79%, more preferably more than 81%, and most preferably more than 83% to the sequence as represented in SEQ ID NO 149 (BE98 sequence) in the region spanning positions 7932 to 8271 in the NS5B region as shown in Figure 1.

Preferentially the above-mentioned genomic HCV sequences depict sequences from the coding regions of all the above-mentioned sequences.

According to the nucleotide distance classification system (with said nucleotide distances being calculated as explained above), said sequences of said composition are selected from:

- an HCV genomic sequence being characterized as having a nucleotide distance of less than 0.44, preferably of less than 0.40, most preferably of less than 0.36 to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region

spanning positions 417 to 957 of the Core/E1 region as shown in Figure 4;

- an HCV genomic sequence being characterized having a nucleotide distance of less than 0.53, preferably less than 0.49, most preferably of less than 0.45 to any of the sequences as represented in SEQ ID NO 19, 21, 23, 25 or 27 in the region spanning positions 574 to 957 of the E1 region as shown in Figure 4:
- an HCV genomic sequence characterized having a nucleotide distance of less than 0.15, preferably less than 0.13, and most preferably less than 0.11 to any of the sequences as represented in SEQ ID NO 147 in the region spanning positions 1 to 378 of the Core region as shown in Figure 3;
- an HCV genomic sequence of HVC type 3a being characterized as having a nucleotide distance of less than 0.3, preferably less than 0.26, most preferably of less than 0.22 to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region spanning positions 417 to 957 in the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence of HCV type 3a being characterized as having a nucleotide distance of less than 0.35, preferably less than 0.31, most preferably of less than 0.27 to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region spanning positions 574 to 957 in the E1 region as shown in Figure 4;
- an HCV genomic sequence of the BR36 subgroup of HCV type 3a being characterized as having a nucleotide sequence of less than 0.0423, preferably less than 0.042, preferably less than 0.0362 to any of the sequences as represented in SEQ ID NO 5, 7, 1, 3, 9 or 11 in the region spanning positions 8023 to 8235 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence of HCV type 3c being characterized as having a nucleotide distance of less than 0.255, preferably of less than 0.25, more preferably of less than 0.21, most preferably of less than 0.17 to the sequence as represented in SEQ ID NO 149 in the region spanning positions 7932 to 8271 in the NS5B region as shown in Figure 1.

In the present application, the E1 sequences encoding the antigenic ectodomain of the E1 protein, which does not overlap the carboxyterminal signal-anchor sequences of E1 disclosed by Cha et al. (1992; WO 92/19743), in addition to the NS4 epitope region, and a part of the NS5 region are disclosed for 4 different isolates: BR33, BR34, BR36, HCCl53 and HD10, all belonging to type 3a (SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 35, 37 or 39).

Also within the present invention are new subtype 3c sequences (SEQ ID NO 147, 149 of the isolate BE98 in the Core and NS5 regions (see Figures 3 and 1).

Finally the present invention also relates to a new subtype 3a sequence as represented in SEQ ID NO 217 (see Figure 1)

Also included within the present invention are sequence variants of the polynucleic acids as selected from any of the nucleotide sequences as given in any of the above mentioned SEQ ID numbers, with said sequence variants containing either deletions and/or insertions of one or more nucleotides, mainly at the extremities of oligonucleotides (either 3' or 5'), or substitutions of some non-essential nucleotides by others (including modified nucleotides an/or inosine), for example, a type 1 or 2 sequence might be modified into a type 3 sequence by replacing some nucleotides of the type 1 or 2 sequence with type-specific nucleotides of type 3 as shown in Figure 1 (NS5 region), Figure 3 (Core region), Figure 4 (Core/E1 region), Figure 6 and 10 (NS3/NS4 region).

According to another embodiment, the present invention relates to a polynucleic acid composition as defined above, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV type 5 genomic sequences:

- an HCV genomic sequence as having a homology of more than 85%, preferably more than 86%, most preferably more than 87% homology to any of the sequences as represented in SEQ ID NO 41, 43, 45, 47, 49, 51, 53 (PC sequences) or 151 (BE95 sequence) in the region spanning positions 1 to 573 of the Core region as shown in Figure 9 and 3;
- an HCV genomic sequence as having a homology of more than 61%, preferably more than 63%, more preferably more than 65% homology, even more preferably more than 66% homology and most preferably more than 67% homology (f.i. 69 and 71%) to any of the sequences as represented in SEQ ID NO 41, 43, 45, 47, 49, 51, 53 (PC sequences), 153 or 155 (BE95, BE100 sequences) in the region spanning positions 574 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence having a homology of more than 76.5%, preferably of more than 77%, most preferably of more than 78% homology with any of the sequences as represented in SEQ ID NO 55, 57, 197 or 199 (PC sequences) in the region spanning positions 3856 to 4209 of the NS3 region as shown in Figure 6 or 10;
- an HCV genomic sequence having a homology of more than 68%, preferably of more than 70%, most preferably of more than 72% homology with the sequence as represented in SEQ ID NO 157 (BE95 sequence) in the region spanning positions 980 to 1179 of the E1/E2 region as shown in Figure 13;
- an HCV genomic sequence having a homology of more than 57%, preferably more than

59%, most preferably more than 61% homology to any of the sequences as represented in SEQ ID NO 59 or 61 (PC sequences) in the region spanning positions 4936 to 5296 of the NS4 region as shown in Figure 6 or 10;

- an HCV genomic sequence as having a homology of more than 93%, preferably more than 93.5%, most preferably more than 94% homology to any of the sequences as represented in SEQ ID NO 159 or 161 (BE95 or BE96 sequences) in the region spanning positions 7932 to 8271 of the NS5B region as shown in Figure 1.

Preferentially the above-mentioned genomic HCV sequences depict sequences from the coding regions of all the above-mentioned sequences.

According to the nucleotide distance classification system (with said nucleotide distances being calculated as explained above), said sequences of said composition are selected from:

- a nucleotide distance of less than 0.53, preferably less than 0.51, more preferably less than 0.49 for the E1 region to the type 5 sequences depicted above;
- a nucleotide distance of less than 0.3, preferably less than 0.28, more preferably of less than 0.26 for the Core region to the type 5 sequences depicted above;
- a nucleotide distance of less than 0.072, preferably less than 0.071, more preferably less than 0.070 for the NS5B region to the type 5 sequences as depicted above.

Isolates with similar sequences in the 5'UR to a group of isolates including SA1, SA3, and SA7 described in the 5'UR by Bukh et al. (1992), have been reported and described in the 5'UR and NS5 region as group V by Cha et al. (1992; WO 92/19743). This group of isolates belongs to type 5a as described in the present invention (SEQ ID NO 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 151, 153, 155, 157, 159, 161, 197 and 199).

Also included within the present invention are sequence variants of the polynucleic acids as selected from any of the nucleotide sequences as given in any of the above given SEQ ID numbers with said sequence variants containing either deletion and/or insertions of one or more nucleotides, mainly at the extremities of oligonucleotides (either 3' or 5'), or substitutions of some non-essential nucleotides (i.e. nucleotides not essential to discriminate between different genotypes of HCV) by others (including modified nucleotides an/or inosine), for example, a type 1 or 2 sequence might be modified into a type 5 sequence by replacing some nucleotides of the type 1 or 2 sequence with type-specific nucleotides of type 5 as shown in Figure 3 (Core region), Figure 4 (Core/E1 region), Figure 10 (NS3 / NS4 region), Figure 14 (E1/E2 region).

Another group of isolates including BU74 and BU79 having similar sequences in the 5'UR to isolates including Z6 and Z7 as described in the 5'UR by Bukh et al. (1992), have been described in the 5'UR and classified as a new type 4 by the inventors of this application (Stuyver et al., 1993). Coding sequences, including core, E1 and NS5 sequences of several new Gabonese isolates belonging to this group, are disclosed in the present invention (SEQ ID NO 106, 108, 110, 112, 114, 116, 118, 120 and 122).

According to yet another embodiment, the present invention relates to a composition as defined above, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV type 4 genomic sequences:

- an HCV genomic sequence having a homology of more than 66%, preferably more than 68%, most preferably more than 70% homology in the E1 region spanning positions 574 to 957 to any of the sequences as represented in SEQ ID NO 118, 120 or 122 (GB358, GB549, GB809 sequences) as shown in Figure 4:
- an HCV genomic sequence having a homology of more than 71%, preferably more than 72%, most preferably more than 74% homology to any of the sequences as represented in SEQ ID NO 118, 120 or 122 (GB358, GB549, GB809 sequences) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence having a homology of more than 92%, preferably more than 93%, most preferably more than 94% homology to any of the sequences as represented in SEQ ID NO 163 or 165 (GB809, CAM600 sequences) in the region spanning positions 1 to 378 of the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4c) having a homology of more than 85%, preferably more than 86%, more preferably more than 86.5% homology, most preferably more than 87, more than 88 or more than 89% homology to any of the sequences as represented in SEQ ID NO 183, 185 or 187 (GB116, GB215, GB809 sequences) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4a) having a homology of more than 81%, preferably more than 83%, most preferably more than 85% homology to the sequence as represented in SEQ ID NO 189 (GB908 sequence) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4e) having a homology of more than 85%, preferably more than 87%, most preferably more than 89% homology to any of the sequences as represented in SEQ ID NO 167 or 169 (CAM600, GB908 sequences) in the region

spanning positions 379 to 957 of the E1 region as shown in Figure 4;

- an HCV genomic sequence (subtype 4f) having a homology of more than 79%, preferably more than 81%, most preferably more than 83% homology to any of the sequences as represented in SEQ ID NO 171 or 173 (CAMG22, CAMG27 sequences) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4g) having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ ID NO 175 (GB549 sequence) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4h) having a homology of more than 83%, preferably more than 85%, most preferably more than 87% homology to the sequence as represented in SEQ ID NO 177 (GB438 sequence) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4i) as having a homology of more than 76%, preferably more than 78%, most preferably more than 80% homology to the sequence as represented in SEQ ID NO 179 (CAR4/1205 sequence) in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4j?) having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ ID NO 181 (CAR4/901 sequence) in the region spanning positions 379 to 957 of the E1 region as shown in figure 4;
- an HCV genomic sequence as having a homology of more than 73%, preferably more than 75%, most preferably more than 77% homology to any of the sequences as represented in SEQ ID NO 106, 108, 110, 112, 114, or 116 (GB48, GB116, GB215, GB358, GB549, GB809 sequences) in the region spanning positions 7932 to 8271 of the NS5 region as shown in figure 1;
- an HCV genomic sequence (subtype 4c) having a homology of more than 88%, preferably more than 89%, most preferably more than 90% homology to any of the sequences as represented in SEQ ID NO 106, 108, 110, or 112 (GB48, GB116, GB215, GB358 sequences) in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4e) having a homology of more than 88%, preferably more than 89%, most preferably more than 90% homology to any of the sequences as

represented in SEQ ID NO 116 or 201 (GB809 or CAM 600 sequences) in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;

- an HCV genomic sequence (subtype 4f) having a homology of more than 87%, preferably more than 89%, most preferably more than 90% homology to the sequence as represented in SEQ ID NO 203 (CAMG22 sequence) in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4g) as having a homology of more than 85%, preferably more than 87%, most preferably more than 89% homology to the sequence as represented in SEQ ID NO 114 (GB549 sequence) in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4h) as having a homology of more than 86%, preferably more than 87%, more preferably more than 88% homology, more preferably more than 89% homology to the sequence as represented in SEQ ID NO 207 (GB437 sequence) in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4i) having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ ID NO 209 (CAR4/1205 sequence) in the region spanning positions 7932 to 8271 of the NS5 region as shown in figure 1;
- an HCV genomic sequence (subtype 4j) having a homology of more than 81%, preferably more than 83%, most preferably more than 85% homology to the sequence as represented in SEQ ID NO 211 (CAR1/501 sequence) in the region spanning positions 7932 to 8271 of the NS5 region as shown in figure 1.

Preferentially the above-mentioned genomic HCV sequences depict sequences from the coding regions of all the above-mentioned sequences.

According to the nucleotide distance classification system (with said nucleotide distances being calculated as explained above), said sequences of said composition are selected from:

- an HCV genomic sequence (type 4) being characterized as having a nucleotide distance of less than 0.52, 0.50, 0.4880, 0.46, 0.44, 0.43 or most preferably less than 0.42 in the region spanning positions 574 to 957 to any of the sequences as represented in SEQ ID NO 118, 120 or 122 in the region spanning positions 1 to 957 of the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence (type 4) being characterized as having a nucleotide distance of

less than 0.39, 0.36 0.34 0.32 or most preferably less than 0.31 to any of the sequences as represented in SEQ ID NO 118, 120 or 122 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;

- an HCV genomic sequence (subtype 4c) being characterized as having a nucleotide distance of less than 0.27, 0.26, 0.24, 0.22, 0.20, 0.18, 0.17, 0.162, 0.16 or most preferably less than 0.15 to any of the sequences as represented in SEQ ID NO 183, 185 or 187 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4a) being characterized as having a nucleotide distance of less than 0.30, 0.28, 0.26, 0.24, 0.22, 0.21 or most preferably of less than 0.205 to the sequence as represented in SEQ ID NO 189 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4e) being characterized as having a nucleotide distance of less than 0.26, 0.25, 0.23, 0.21, 0.19, 0.17, 0.165, most preferably less than 0.16 to any of the sequences as represented in SEQ ID NO 167 or 169 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4f) being characterized as having a nucleotide distance of less than 0.26, 0.24, 0.22, 0.20, 0.18, 0.16, 0.15 or most preferably less than 0.14 to any of the sequences as represented in SEQ ID NO 171 or 173 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4g) being characterized as having a nucleotide distance of less than 0.20, 0.19, 0.18, 0.17 or most preferably of less than 0.16 to the sequence as represented in SEQ ID NO 175 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4h) being characterized as having a nucleotide distance of less than 0.20, 0.19, 0.18, 0.17 and most preferably of less than 0.16 to the sequence as represented in SEQ ID NO 177 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4i) being characterized as having a nucleotide distance of less than 0.27, 0.25, 0.23, 0.21 and preferably less than 0.16 to the sequence as represented in SEQ ID NO 179 in the region spanning positions 379 to 957 of the E1 region as shown in Figure 4;
- an HCV genomic sequence (subtype 4j?) being characterized as having a nucleotide distance of less than 0.19, 0.18, 0.17, 0.165 and most preferably of less than 0.16 to the

- sequence as represented in SEQ ID NO 181 in the region spanning positions 379 to 957 of the E1 region as shown in figure 4;
- an HCV genomic sequence (type 4) being characterized as having a nucleotide distance of less than 0.35, 0.34, 0.32 and most preferably of less than 0.30 to any of the sequences as represented in SEQ ID NO 106, 108, 110, 112, 114, or 116 in the region spanning positions 7932 to 8271 of the NS5 region as shown in figure 1;
- an HCV genomic sequence (subtype 4c) being characterized as having a nucleotide distance of less than 0.18, 0.16, 0.14, 0.135, 0.13, 0.1275 or most preferably less than 0.125 to any of the sequences as represented in SEQ ID NO 106, 108, 110, or 112 in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4e) being characterized as having a nucleotide distance of less than 0.15, 0.14, 0.135, 0.13 and most preferably of less than 0.125 to any of the sequences as represented in SEQ ID NO 116 or 201 in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4f) being characterized as having a nucleotide distance of less than 0.15, 0.14, 0.135, 0.13 or most preferably less than 0.125 to the sequence as represented in SEQ ID NO 203 in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4g) being characterized as having a nucleotide distance of less than 0.17, 0.16, 0.15, 0.14, 0.13 or most preferably less than 0.125 to the sequence as represented in SEQ ID NO 114 in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4h) being characterized as having a nucleotide distance of less than 0.155, 0.15, 0.145, 0.14, 0.135, 0.13 or most preferably less than 0.125 to the sequence as represented in SEQ ID NO 207 in the region spanning positions 7932 to 8271 of the NS5 region as shown in Figure 1;
- an HCV genomic sequence (subtype 4i) being characterized as having a nucleotide distance of less than 0.17, 0.16, 0.15, 0.14, 0.13 or most preferably of less than 0.125 to the sequence as represented in SEQ ID NO 209 in the region spanning positions 7932 to 8271 of the NS5 region as shown in figure 1;
- an HCV genomic sequence (subtype 4j) being characterized as having a nucleotide distance of less than 0.21, 0.20, 0.19, 0.18, 0.17, 0.16, 0.15, 0.14, 0.13 and most preferably of less than 0.125 to the sequence as represented in SEQ ID NO 211 in the region spanning

positions 7932 to 8271 of the NS5 region as shown in figure 1.

Also included within the present invention are sequence variants of the polynucleic acids as selected from any of the nucleotide sequences as given in any of the above given SEQ ID numbers with said sequence variants containing either deletion and/or insertions of one or more nucleotides, mainly at the extremities of oligonucleotides (either 3' or 5'), or substitutions of some non-essential nucleotides (i.e. nucleotides not essential to discriminate between different genotypes of HCV) by others (including modified nucleotides an/or inosine), for example, a type 1 or 2 sequence might be modified into a type 4 sequence by replacing some nucleotides of the type 1 or 2 sequence with type-specific nucleotides of type 4 as shown in Figure 3 (Core region), Figure 4 (Core/E1 region), Figure 10 (NS3 / NS4 region), Figure 14 (E1/E2 region).

The present invention also relates to a sequence as represented in SEQ ID NO 193 (GB724 sequence).

After aligning NS5 or E1 sequences of GB48, GB, 116, GB215, GB358, GB549 and GB809, these isolates clearly segregated into 3 subtypes within type 4: GB48, GB116, GB215 and GB358 belong to the sybtype designated 4c, GB549 to subtype 4g and GB809 to subtype 4e. In NS5, GB809 (subtype 4e) showed a higher nucleic acids homology to subtype 4c isolates (85.6 - 86.8%) than to GB549 (subtype 4g, 79.7%), while GB549 showed similar homologies to both other subtypes (78.8 to 80% to subtype 4c and 79.7% to subtype 4e). In E1, subtype 4c showed equal nucleic acid homologies of 75.2% to subtypes 4g and 4e while 4g and 4e were 78.4% homologous. At the amino acid level however, subtype 4e showed a normal homology to subtype 4c (80.2%), while subtype 4g was more homologous to 4c (83.3%) and 4e (84.1%).

According to yet another embodiment, the present invention relates to a composition as defined above, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV type 2d genomic sequences:

- an HCV genomic sequence as having a homology of more than 78%, preferably more than 80%, most preferably more than 82% homology to the sequence as represented in SEQ ID NO (NE92) 143 in the region spanning positions 379 to 957 of the Core/E1 region as shown in Figure 4;
- an HCV genomic sequence as having a homology of more than 74%, preferably more than 76%, most preferably more than 78% homology to the sequence as represented in SEQ ID NO 143 (NE92) in the region spanning positions 574 to 957 as shown in Figure 4;

- an HCV genomic sequence as having a homology of more than 87%, preferably more than 89%, most preferably more than 91% homology to the sequence as represented in SEQ ID NO 145 (NE92) in the region spanning positions 7932 to 8271 of the NS5B region as shown in Figure 1.

Preferentially the above-mentioned genomic HCV sequences depict sequences from the coding regions of all the above-mentioned sequences.

According to the nucleotide distance classification system (with said nucleotide distances being calculated as explained above), said sequences of said composition are selected from:

- a nucleotide distance of less than 0.32, preferably less than 0.31, more preferably less than 0.30 for the E1 region (574 to 957) to any of the above specified sequences;
- a nucleotide distance of less than 0.08, preferably less than 0.07, more preferably less than 0.06 for the Core region (1 to 378) to any of the above given sequences
- a nucleotide distance of less than 0.15, preferentially less than 0.13, more preferentially less than 0.12 for the NS5B region to any of the above-specified sequences.

Polynucleic acid sequences according to the present invention which are homologous to the sequences as represented by a SEQ ID NO can be characterized and isolated according to any of the techniques known in the art, such as amplification by means of type or subtype specific primers, hybridization with type or subtype specific probes under more or less stringent conditions, serological screening methods (see examples 4 and 11) or via the LiPA typing system.

Polynucleic acid sequences of the genomes indicated above from regions not yet depicted in the present examples, figures and sequence listing can be obtained by any of the techniques known in the art, such as amplification techniques using suitable primers from the type or subtype specific sequences of the present invention.

The present invention relates also to a composition as defined above, wherein said polynucleic acid is liable to act as a primer for amplifying the nucleic acid of a certain isolate belonging to the genotype from which the primer is derived.

An example of a primer according to this embodiment of the invention is HCPr 152 as shown in table 7 (SEQ ID NO 79).

The term "primer" refers to a single stranded DNA oligonucleotide sequence capable of acting as a point of initiation for synthesis of a primer extension product which is complementary to the nucleic acid strand to be copied. The length and the sequence of the primer must be such that they allow to prime the synthesis of the extension products.

Preferably the primer is about 5-50 nucleotides. Specific length and sequence will depend on the complexity of the required DNA or RNA targets, as well as on the conditions of primer use such as temperature and ionic strength.

The fact that amplification primers do not have to match exactly with corresponding template sequence to warrant proper amplification is amply documented in the literature (Kwok et al., 1990).

The amplification method used can be either polymerase chain reaction (PCR; Saiki et al., 1988), ligase chain reaction (LCR; Landgren et al., 1988; Wu & Wallace, 1989; Barany, 1991), nucleic acid sequence-based amplification (NASBA; Guatelli et al., 1990; Compton, 1991), transcription-based amplification system (TAS; Kwoh et al., 1989), strand displacement amplification (SDA; Duck, 1990; Walker et al., 1992) or amplification by means of QB replicase (Lizardi et al., 1988; Lomeli et al., 1989) or any other suitable method to amplify nucleic acid molecules using primer extension. During amplification, the amplified products can be conveniently labelled either using labelled primers or by incorporating labelled nucleotides. Labels may be isotopic (32P, 33S, etc.) or non-isotopic (biotin, digoxigenin, etc.). The amplification reaction is repeated between 20 and 80 times, advantageously between 30 and 50 times.

The present invention also relates to a composition as defined above, wherein said polynucleic acid is able to act as a hybridization probe for specific detection and/or classification into types of a nucleic acid containing said nucleotide sequence, with said oligonucleotide being possibly labelled or attached to a solid substrate.

The term "probe" refers to single stranded sequence-specific oligonucleotides which have a sequence which is complementary to the target sequence of the HCV genotype(s) to be detected.

Preferably, these probes are about 5 to 50 nucleotides long, more preferably from about 10 to 25 nucleotides.

The term "solid support" can refer to any substrate to which an oligonucleotide probe can be coupled, provided that it retains its hybridization characteristics and provided that the background level of hybridization remains low. Usually the solid substrate will be a microtiter plate, a membrane (e.g. nylon or nitrocellulose) or a microsphere (bead). Prior to application to the membrane or fixation it may be convenient to modify the nucleic acid probe in order to facilitate fixation or improve the hybridization efficiency. Such modifications may encompass homopolymer tailing, coupling with different reactive groups such as aliphatic

groups, NH<sub>2</sub> groups, SH groups, carboxylic groups, or coupling with biotin or haptens.

The present invention also relates to the use of a composition as defined above for detecting the presence of one or more HCV genotypes, more particularly for detecting the presence of a nucleic acid of any of the HCV genotypes having a nucleotide sequence as defined above, present in a biological sample liable to contain them, comprising at least the following steps:

- (i) possibly extracting sample nucleic acid.
- (ii) possibly amplifying the nucleic acid with at least one of the primers as defined above or any other HCV subtype 2d, HCV type 3, HCV type 4, HCV type 5 or universal HCV primer,
- hybrizing the nucleic acids of the biological sample, possibly under denatured conditions, and with said nucleic acids being possibly labelled during or after amplification, at appropriate conditions with one or more probes as defined above, with said probes being preferably attached to a solid substrate,
- (iv) washing at appropriate conditions,
- (v) detecting the hybrids formed,
- (vi) inferring the presence of one or more HCV genotypes present from the observed hybridization pattern.

Preferably, this technique could be performed in the Core or NS5B region.

The term "nucleic acid" can also be referred to as analyte strand and corresponds to a single- or double-stranded nucleic acid molecule. This analyte strand is preferentially positive-or negative stranded RNA, cDNA or amplified cDNA.

The term "biological sample" refers to any biological sample (tissue or fluid) containing HCV nucleic acid sequences and refers more particularly to blood serum or plasma samples.

The term "HCV subtype 2d primer" refers to a primer which specifically amplifies HCV subtype 2d sequences present in a sample (see Examples section and figures).

The term "HCV type 3 primer" refers to a primer which specifically amplifies HCV type 3 sequences present in a sample (see Examples section and figures).

The term "HCV type 4 primer" refers to a primer which specifically amplifies HCV type 4 genomes present in a sample.

The term "universal HCV primer" refers to oligonucleotide sequences complementary to any of the conserved regions of the HCV genome.

The term "HCV type 5 primer" refers to a primer which specifically amplifies HCV type

5 genomes present in a sample. The term "universal HCV primer" refers to oligonucleotide sequences complementary to any of the conserved regions of the HCV genome.

The expression "appropriate" hybridization and washing conditions are to be understood as stringent and are generally known in the art (e.g. Maniatis et al., Molecular Cloning: A Laboratory Manual, New York, Cold Spring Harbor Laboratory, 1982).

However, according to the hybridization solution (SSC, SSPE, etc.), these probes should be hybridized at their appropriate temperature in order to attain sufficient specificity.

The term "labelled" refers to the use of labelled nucleic acids. This may include the use of labelled nucleotides incorporated during the polymerase step of the amplification such as illustrated by Saiki et al. (1988) or Bej et al. (1990) or labelled primers, or by any other method known to the person skilled in the art.

The process of the invention comprises the steps of contacting any of the probes as defined above, with one of the following elements:

- either a biological sample in which the nucleic acids are made available for hybridization,
- or the purified nucleic acids contained in the biological sample
- or a single copy derived from the purified nucleic acids,
- or an amplified copy derived from the purified nucleic acids, with said elements or with said probes being attached to a solid substrate.

The expression "inferring the presence of one or more HCV genotypes present from the observed hybridization pattern" refers to the identification of the presence of HCV genomes in the sample by analyzing the pattern of binding of a panel of oligonucleotide probes. Single probes may provide useful information concerning the presence or absence of HCV genomes in a sample. On the other hand, the variation of the HCV genomes is dispersed in nature, so rarely is any one probe able to identify uniquely a specific HCV genome. Rather, the identity of an HCV genotype may be inferred from the pattern of binding of a panel of oligonucleotide probes, which are specific for (different) segments of the different HCV genomes. Depending on the choice of these oligonucleotide probes, each known HCV genotype will correspond to a specific hybridization pattern upon use of a specific combination of probes. Each HCV genotype will also be able to be discriminated from any other HCV genotype amplified with the same primers depending on the choice of the oligonucleotide probes. Comparison of the generated pattern of positively hybridizing probes for a sample containing one or more unkown HCV sequences to a scheme of expected

hybridization patterns, allows one to clearly infer the HCV genotypes present in said sample.

The present invention thus relates to a method as defined above, wherein one or more hybridization probes are selected from any of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59 or 61, 106, 108, 110, 112, 114, 116, 118, 120, 122, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 198, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 222, 269 or sequence variants thereof, with said sequence variants containing deletions and/or insertions of one or more nucleotides, mainly at their extremities (either 3' or 5'), or substitutions of some non-essential nucleotides (i.e. nucleotides not essential to discriminate between genotypes) by others (including modified nucleotides or inosine), or with said variants consisting of the complement of any of the above-mentioned oligonucleotide probes, or with said variants consisting of ribonucleotides instead of deoxyribonucleotides, all provided that said variant probes can be caused to hybridize with the same specificity as the oligonucleotide probes from which they are derived.

In order to distinguish the amplified HCV genomes from each other, the target polynucleic acids are hybridized to a set of sequence-specific DNA probes targetting HCV genotypic regions located in the HCV polynucleic acids.

Most of these probes target the most type-specific regions of HCV genotypes, but some can be caused to hybridize to more than one HCV genotype.

According to the hybridization solution (SSC, SSPE, etc.), these probes should be stringently hybridized at their appropriate temperature in order to attain sufficient specificity. However, by slightly modifying the DNA probes, either by adding or deleting one or a few nucleotides at their extremities (either 3' or 5'), or substituting some non-essential nucleotides (i.e. nucleotides not essential to discriminate between types) by others (including modified nucleotides or inosine) these probes or variants thereof can be caused to hybridize specifically at the same hybridization conditions (i.e. the same temperature and the same hybridization solution). Also changing the amount (concentration) of probe used may be beneficial to obtain more specific hybridization results. It should be noted in this context, that probes of the same length, regardless of their GC content, will hybridize specifically at approximately the same temperature in TMACl solutions (Jacobs et al., 1988).

Suitable assay methods for purposes of the present invention to detect hybrids formed between the oligonucleotide probes and the nucleic acid sequences in a sample may comprise

any of the assay formats known in the art, such as the conventional dot-blot format, sandwich hybridization or reverse hybridization. For example, the detection can be accomplished using a dot blot format, the unlabelled amplified sample being bound to a membrane, the membrane being incorporated with at least one labelled probe under suitable hybridization and wash conditions, and the presence of bound probe being monitored.

An alternative and preferred method is a "reverse" dot-blot format, in which the amplified sequence contains a label. In this format, the unlabelled oligonucleotide probes are bound to a solid support and exposed to the labelled sample under appropriate stringent hybridization and subsequent washing conditions. It is to be understood that also any other assay method which relies on the formation of a hybrid between the nucleic acids of the sample and the oligonucleotide probes according to the present invention may be used.

According to an advantageous embodiment, the process of detecting one or more HCV genotypes contained in a biological sample comprises the steps of contacting amplified HCV nucleic acid copies derived from the biological sample, with oligonucleotide probes which have been immobilized as parallel lines on a solid support.

According to this advantageous method, the probes are immobilized in a Line Probe Assay (LiPA) format. This is a reverse hybridization format (Saiki et al., 1989) using membrane strips onto which several oligonucleotide probes (including negative or positive control oligonucleotides) can be conveniently applied as parallel lines.

The invention thus also relates to a solid support, preferably a membrane strip, carrying on its surface, one or more probes as defined above, coupled to the support in the form of parallel lines.

The LiPA is a very rapid and user-friendly hybridization test. Results can be read 4 h. after the start of the amplification. After amplification during which usually a non-isotopic label is incorporated in the amplified product, and alkaline denaturation, the amplified product is contacted with the probes on the membrane and the hybridization is carried out for about 1 to 1,5 h hybridized polynucleic acid is detected. From the hybridization pattern generated, the HCV type can be deduced either visually, but preferably using dedicated software. The LiPA format is completely compatible with commercially available scanning devices, thus rendering automatic interpretation of the results very reliable. All those advantages make the LiPA format liable for the use of HCV detection in a routine setting. The LiPA format should be particularly advantageous for detecting the presence of different HCV genotypes.

The present invention also relates to a method for detecting and identifying novel HCV

genotypes, different from the known HCV genomes, comprising the steps of:

- determining to which HCV genotype the nucleotides present in a biological sample belong, according to the process as defined above,
- in the case of observing a sample which does not generate a hybridization pattern compatible with those defined in Table 3, sequencing the portion of the HCV genome sequence corresponding to the aberrantly hybridizing probe of the new HCV genotype to be determined.

The present invention also relates to the use of a composition as defined above, for detecting one or more genotypes of HCV present in a biological sample liable to contain them, comprising the steps of:

- (i) possibly extracting sample nucleic acid,
- (ii) amplifying the nucleic acid with at least one of the primers as defined above,
- (iii) sequencing the amplified products
- (iv) inferring the HCV genotypes present from the determined sequences by comparison to all known HCV sequences.

The present invention also relates to a composition consisting of or comprising at least one peptide or polypeptide comprising a contiguous sequence of at least 5 amino acids corresponding to a contiguous amino acid sequence encoded by at least one of the HCV genomic sequences as defined above, having at least one amino acid differing from the corresponding region of known HCV (type 1 and/or type 2 and/or type 3) polyprotein sequences as shown in Table 3, or muteins thereof.

It is to be noted that, at the level of the amino acid sequence, an amino acid difference (with respect to known HCV amino acid sequences) is necessary, which means that the polypeptides of the invention correspond to polynucleic acids having a nucleotide difference (with known HCV polynucleic acid sequences) involving an amino acid difference.

The new amino acid sequences, as deduced from the disclosed nucleotide sequences (see SEQ ID NO 1 to 62 and 106 to 123 and 143 to 218, 223 and 270), show homologies of only 59.9 to 78% with prototype sequences of type 1 and 2 for the NS4 region, and of only 53.9 to 68.8% with prototype sequences of type 1 and 2 for the E1 region. As the NS4 region is known to contain several epitopes, for example characterized in patent application EP-A-0 489 968, and as the E1 protein is expected to be subject to immune attack as part of the viral envelope and expected to contain epitopes, the NS4 and E1 epitopes of the new type 3, 4 and 5 isolates will consistently differ from the epitopes present in type 1 and 2 isolates. This is

examplified by the type-specificity of NS4 synthetic peptides as presented in example 4, and the type-specificity of recombinant E1 proteins in example 11.

After aligning the new subtype 2d, type 3, 4 and 5 (see SEQ ID NO 1 to 62 and 106 to 123 and 143 to 218, 223 and 270) amino acid sequences with the prototype sequences of type 1a, 1b, 2a, and 2b, type- and subtype-specific variable regions can be delineated as presented in Figure 5 and 7.

As to the muteins derived from the polypeptides of the invention, Table 4 gives an overview of the amino acid substitutions which could be the basis of some of the muteins as defined above.

The peptides according to the present invention contain preferably at least 5 contiguous HCV amino acids, preferably however at least 8 contiguous amino acids, at least 10 or at least 15 (for instance at least 9, 11, 12, 13, 14, 20 or 25 amino acids) of the new HCV sequences of the invention.

TABLE 4

Amino acids	Synonymous groups		
Ser (S)	Ser, Thr, Gly, Asn		
Arg (R)	Arg, His, Lys, Glu, Gln		
Leu (L)	Leu; Ile, Met, Phe, Val, Tyr		
Pro (P)	Pro, Ala, Thr, Gly		
Thr (T)	Thr, Pro, Ser, Ala, Gly, His, Gln		
Ala (A)	Ala, Pro, Gly, Thr		
Val (V)	Val, Met, Ile, Tyr, Phe, Leu, Val		
Gly (G)	Gly, Ala, Thr, Pro, Ser		
Ile (I)	Ile, Met, Leu, Phe, Val, Ile, Tyr		
Phe (F)	Phe, Met, Tyr, Ile, Leu, Trp, Val		
Tyr (Y)	Tyr, Phe, Trp, Met, Ile, Val, Leu		
Cys (C)	Cys, Ser, Thr, Met		
His (H)	His, Gln, Arg, Lys, Glu, Thr		
Gln (Q)	Gln, Glu, His, Lys, Asn, Thr, Arg		
Asn (N)	Asn, Asp, Ser, Gln		
Lys (K)	Lys, Arg, Glu, Gln, His		
Asp (D)	Asp, Asn, Glu, Gln		
Glu (E)	Glu, Gln, Asp, Lys, Asn, His, Arg		
Met (M)	Met, Ile, Leu, Phe, Val		

The polypeptides of the invention, and particularly the fragments, can be prepared by classical chemical synthesis.

The synthesis can be carried out in homogeneous solution or in solid phase.

For instance, the synthesis technique in homogeneous solution which can be used is the one described by Houbenweyl in the book entitled "Methode der organischen chemie" (Method of organic chemistry) edited by E. Wunsh, vol. 15-I et II. THIEME, Stuttgart 1974.

The polypeptides of the invention can also be prepared in solid phase according to the methods described by Atherton and Shepard in their book entitled "Solid phase peptide synthesis" (IRL Press, Oxford, 1989).

The polypeptides according to this invention can be prepared by means of recombinant DNA techniques as described by Maniatis et al., Molecular Cloning: A Laboratory Manual, New York, Cold Spring Harbor Laboratory, 1982).

The present invention relates particularly to a polypeptide or peptide composition as defined above, wherein said contiguous sequence contains in its sequence at least one of the following amino acid residues:

L7, Q43, M44, S60, R67, Q70, T71, A79, A87, N106, K115, A127, A190, S130, V134, G142, I144, E152, A157, V158, P165, S177 or Y177, I178, V180 or E180 or F182, R184, I186, H187, T189, A190, S191 or G191, Q192 or L192 or I192 or V192 or E192, N193 or H193 or P193, W194 or Y194, H195, A197 or I197 or V197 or T197, V202, I203 or L203, Q208, A210, V212, F214, T216, R217 or D217 or E217 or V217, H218 or N218, H219 or V219 or L219, L227 or I227, M231 or E231 or Q231, T232 or D232 or A232 or K232, Q235 or I235, A237 or T237, I242, I246, S247, S248, V249, S250 or Y250, I251 or V251 or M251 or F251, D252, T254 or V254, L255 or V255, E256 or A256, M258 or F258 or V258, A260 or Q260 or S260, A261, T264 or Y264, M265, I266 or A266, A267, G268 or T268, F271 or M271 or V271, I277, M280 or H280, I284 or A284 or L84, V274, V291, N292 or S292, R293 or I293 or Y293, Q294 or R294, L297 or I297 or Q297, A299 or K299 or Q299, N303 or T303, T308 or L308, T310 or F310 or A310 or D310 or V310, L313, G317 or Q317, L333, S351, A358, A359, A363, S364, A366, T369, L373, F376, Q386, I387, S392, I399, F402, I403, R405, D454, A461, A463, T464, K484, Q500, E501, S521, K522, H524, N528, S531, S532, V534, F536, F537, M539, I546, C1282, A1283, H1310, V1312, Q1321, P1368, V1372, V1373, K1405, Q1406, S1409, A1424, A1429, C1435, S1436, S1456, H1496, A1504, D1510, D1529, I1543, N1567, D1556, N1567, M1572, Q1579, L1581, S1583, F1585, V1595, E1606 or T1606, M1611, V1612 or L1612, P1630, C1636, P1651, T1656 or I1656, L1663, V1667, V1677, A1681, H1685, E1687, G1689, V1695, A1700, Q1704, Y1705, A1713, A1714 or S1714, M1718, D1719, A1721 or T1721, R1722, A1723 or V1723, H1726 or G1726, E1730, V1732, F1735, I1736, S1737, R1738, T1739, G1740, Q1741, K1742, Q1743, A1744, T1745, L1746, E1747 or K1747, I1749, A1750, T1751 or A1751, V1753, N1755, K1756, A1757, P1758, A1759, H1762, T1763, Y1764, P2645, A2647, K2650, K2653 or L2653, S2664, N2673, F2680, K2681, L2686, H2692, Q2695 or L2695 or I2695, V2712, F2715, V2719 or Q2719, T2722, T2724, S2725, R2726, G2729, Y2735, H2739, I2748, G2746 or I2746, I2748, P2752 or K2752, P2754 or T2754, T2757 or P2757.

with said notation being composed of a letter representing the amino acid residue by its oneletter code, and a number representing the amino acid numbering according to Kato et al., 1990 as shown in Table 1 (comparison with other isolates). See also the numbering in Figures 2, 5, 7, and 11 (alignment amino acid sequences).

Within the group of unique and new amino acid residues of the present invention, the following residues were found to be specific for the following types of HCV according to the

HCV classification system used in the present invention:

- Q208, R217, E231, I235, I246, T264, I266, A267, F271, K299, L2686, Q2719 which are specific for the HCV subtype 2d sequences of the present invention as shown in Fig. 5 and 2;
- Q43, S60, R67, F182, I186, H187, A190, S191, L192, W194, V202, L203, V219,
   Q231, D232, A237, T254, M280, Q299, T303, L308, and/or L313 which are specific for the Core/E1 region of HCV type 3 of the invention as shown in Fig. 5;
- D1556, Q1579, L1581, S1584, F1585, E1606, V1612, P1630, C1636, T1656, L1663, H1685, E1687, G1689, V1695, Y1705, A1713, A1714, A1721, V1723, H1726, R1738, Q1743, A1744, E1747, I1749, A1751, A1759 and/or H1762 which are specific for the NS3/4 region of HCV type 3 sequences of the invention as shown in Fig. 7;
- K2665, D2666, R2670 which are specific for the NS5B region of HCV type 3 of the invention as shown in Fig. 2;
- L7, A79, A127, S130, E152, V158, S177 or Y177, V180 or E180, R184, T189, Q192 or E192 or I192, N193 or H193, I197 or V197, I203, A210, V212, E217, H218, H219, L227, A232, V249, I251 or M251, D252, L255 or V255, E256, M258 or V258 or F258, A260 or Q260, M265, T268, V271, V274, M280, I284, N292 or S292, Q294, L297 or I297, T308, A310 or D310 or V310 or T310, and G317 which are specific for the core/E1 region of HCV type 4 sequences of the present invention as shown in Fig. 5;
- P2645, K2650, K2653, G2656, V2658, T2668, N2673 or N2673, K2681, H2686,
   D2691, L2692, Q2695 or L2695 or I2695, Y2704, V2712, F2715, V2719, I2722,
   S2725, G2729, Y2735, G2746 or I2746, P2752 or K2752, Q2753, P2754 or
   T2754, T2757 or P2757 which are specific for the NS5B region of the HCV type
   4 sequences of the present invention as shown in Fig. 2;
- M44, Q70, A87, N106, K115, V137, G142, P165, I178, F251, A299, N303, Q317 which are specific for the Core/E1 region of the HCV type 4 sequences of the present invention as shown in Fig. 5;
- L333, S351, A358, A359, A363, S364, A366, T369, L373, F376, Q386, I387, S392, I399, F102, I403, R405, D454, A461, A463, T464, K484, Q500, E501, S521, K522, H524, N528, S532, V534, F537, M539, I546 which are specific for

- the E1/E2 region of the HCV type 5 sequences of the present invention as shown in Fig. 12;
- C1282, A1283, V1312, Q1321, P1368, V1372, K1405, Q1406, S1409, A1424, A1429, C1435, S1436, S1456, H1496, A1504, D1510, D1529, I1543, N1567, M1572, V1595, T1606, M1611, L1612, I1656, V1667, A1681, A1700, A1713, S1714, M1718, D1719, T1721, R1722, A1723, G1726, F1735, I1736, S1737, T1739, G1740, K1742, T1745, L1746, K1747, A1750, V1753, N1755, A1757, D1758, T1763, and Y1764 which are specific for the NS3/NS4 region of HCV type 5 sequences of the invention as shown in Fig. 7;
- A2647, L2653, S2674, F2680, T2724, R2726, Y2730, H2739 which are specific for the NS5B region of the HCV type 5 sequences of the present invention as shown in Fig. 2;
- A256, P1631, V1677, Q1704, E1730, V1732, Q1741 and T1751 which are specific for the HCV type 3 and 5 sequences of the present invention as shown in Fig. 5 and 7;
- T71, A157, I227, T237, T240, Y250, V251, S260, M271, T2673, T2722, I2748 which are specific for the HCV type 3 and 4 sequences of the present invention as shown in Fig. 5 and 2,
- V192, Y194, A197, P249, S250, R294 which are specific for the HCV type 4 and 5 sequences of the present invention as shown in Fig. 5;
- I293 which is specific for the HCV type 4 and subtype 2d sequence of the present invention as shown in Fig. 5;
- D217 and R294 which are specific for the HCV type 3, 4 and 5 sequences of the present invention as shown in Fig. 5;
- L192 which is specific for the HCV type 3 and subtype 2d sequences of the present invention as shown in Fig. 5;
- G191 and T197 which are specific for the HCV type 3, 4 and subtype 2d sequences of the present invention as shown in Fig. 5;
- K232 which is specific for the HCV subtype 2d en type 5 sequences of the present invention as shown in Fig. 5.

and with said notation being composed of a letter, unambiguously representing the amino acid by its one-letter code, and a number representing the amino acid numbering according to Kato et al., 1990 (see also Table 1 for comparison with other isolates), as well as Figure 2 (NS5)

region), Figure 5 (Core/E1 region), Figure 7 (NS3/NS4 region), Figure 12 (E1/E2 region). Some of the above-mentioned amino acids may be contained in type or subtype specific epitopes.

For example M231 (detected in type 5) refers to a methionine at position 231. A glutamine (Q) is present at the same position 231 in type 3 isolates, whereas this position is occupied by an arginine in type 1 isolates and by a lysine (K) or asparagine (N) in type 2 isolates (see Figure 5).

The peptide or polypeptide according to this embodiment of the invention may be possibly labelled, or attached to a solid substrate, or coupled to a carrier molecule such as biotin, or mixed with a proper adjuvant.

The variable region in the core protein (V-CORE in Fig. 5) has been shown to be useful for serotyping (Machida et al., 1992). The sequence of the disclosed type 5 sequence in this region shows type-specific features. The peptide from amino acid 70 to 78 shows the following unique sequence for the sequences of the present inevntion (see figure 5):

QPTGRSWGQ (SEQ ID NO 93)

**RSEGRTSWAQ (SEQ ID NO 220)** 

and RTEGRTSWAQ (SEQ ID NO 221)

Another preferred V-Core spanning region is the peptide spanning positions 60 to 78 of subtype 3c with sequence:

SRRQPIPRARRTEGRSWAQ (SEQ ID NO 268)

Five type-specific variable regions (V1 to V5) can be identified after aligning E1 amino acid sequences of the 4 genotypes, as shown in Figure 5.

Region V1 encompasses amino acids 192 to 203, this is the amino-terminal 10 amino acids of the E1 protein. The following unique sequences as shown in Fig. 5 can be deduced:

LEWRNTSGLYVL (SEQ ID NO 83)

VNYRNASGIYHI (SEQ ID NO 126)

QHYRNISGIYHV (SEQ ID NO 127)

EHYRNASGIYHI (SEQ ID NO 128)

IHYRNASGIYHI (SEQ ID NO 224)

VPYRNASGIYHV (SEQ ID NO 84)

VNYRNASGIYHI (SEQ ID NO 225)

VNYRNASGVYHI (SEQ ID NO 226)

VNYHNTSGIYHL (SEQ ID NO 227)

QHYRNASGIYHV (SEQ ID NO 228) QHYRNVSGIYHV (SEQ ID NO 229) IHYRNASDGYYI (SEQ ID NO 230) LQVKNTSSSYMV (SEQ ID NO 231)

Region V2 encompasses amino acids 213 to 223. The following unique sequences can be found in the V2 region as shown in Figure 5:

VYEADDVILHT (SEQ ID NO 85)

VYETEHHILHL (SEQ ID NO 129)

VYEADHHIMHL (SEQ ID NO 130)

VYETDHHILHL (SEQ ID NO 131)

VYEADNLILHA (SEQ ID NO 86)

VWQLRAIVLHV (SEQ ID NO 232)

VYEADYHILHL (SEQ ID NO 233)

VYETDNHILHL (SEQ ID NO 234)

VYETENHILHL (SEQ ID NO 235)

VFETVHHILHL (SEQ ID NO 236)

VFETEHHILHL (SEQ ID NO 237)

VFETDHHIMHL (SEQ ID NO 238)

VYETENHILHL (SEQ ID NO 239)

VYEADALILHA (SEQ ID NO 240)

Region V3 encompasses the amino acids 230 to 242. The following unique V3 region sequences can be deduced from Figure 5:

VQDGNTSTCWTPV (SEQ ID NO 87)

VQDGNTSACWTPV (SEQ ID NO 241)

VRVGNQSRCWVAL (SEQ ID NO 132)

VRTGNTSRCWVPL (SEQ ID NO 133)

VRAGNVSRCWTPV (SEQ ID NO 134)

EEKGNISRCWIPV (SEQ ID NO 242)

VKTGNQSRCWVAL (SEQ ID NO 243)

VRTGNQSRCWVAL (SEQ ID NO 244)

VKTGNQSRCWIAL (SEQ ID NO 245)

VKTGNVSRCWIPL (SEQ ID NO 247)

VKTGNVSRCWISL (SEQ ID NO 248)

#### VRKDNVSRCWVQI (SEQ ID NO 249)

Region V4 encompasses the amino acids 248 to 257. The following unique V4 region sequences can be deduced from figure 5:

VRYVGATTAS (SEQ ID NO 89)

**APYIGAPLES (SEQ ID NO 135)** 

APYVGAPLES (SEQ ID NO 136)

**AVSMDAPLES (SEQ ID NO 137)** 

APSLGAVTAP (SEQ ID NO 90)

**APSFGAVTAP (SEQ ID NO 250)** 

VSQPGALTKG (SEQ ID NO 251)

VKYVGATTAS (SEQ ID NO 252)

APYIGAPVES (SEQ ID NO 253)

**AQHLNAPLES (SEQ ID NO 254)** 

SPYVGAPLEP (SEQ ID NO 255)

SPYAGAPLEP (SEQ ID NO 256)

APYLGAPLEP (SEQ ID NO 257)

APYLGAPLES (SEQ ID NO 258)

APYVGAPLES (SEQ ID NO 259)

VPYLGAPLTS (SEQ ID NO 260)

APHLRAPLSS (SEQ ID NO 261)

APYLGAPLTS (SEQ ID NO 262)

Region V5 encompasses the amino acids 294 to 303. The following unique V5 region peptides can be deduced from figure 5:

RPRRHQTVQT (SEQ ID NO 91)

QPRRHWTTQD (SEQ ID NO 138)

RPRRHWTTQD (SEQ ID NO 139)

RPRQHATVQN (SEQ ID NO 92)

RPRQHATVQD (SEQ ID NO 263)

SPQHHKFVQD (SEQ ID NO 264)

RPRRLWTTQE (SEQ ID NO 265)

PPRIHETTQD (SEQ ID NO 266)

The variable region in the E2 region (HVR-2) of type 5a as shown in Figure 12 spanning amino acid positions 471 to 484 is also a preferred peptide according to the present invention

with the following sequence:

TISYANGSGPSDDK (SEQ ID NO 267)

The above given list of peptides are particularly suitable for vaccine and diagnostic development.

Also comprised in the present invention is any synthetic peptide or polypeptide containing at least 5 contiguous amino acids derived from the above-defined peptides in their peptidic chain.

According to a specific embodiment, the present invention relates to a composition as defined above, wherein said contiguous sequence is selected from any of the following HCV amino acid type 3 sequences:

- a sequence having a homology of more than 72%, preferably more than 74%, more preferably more than 77% and most preferably more than 80 or 84% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 (HD10, BR36, BR33 sequences) in the region spanning positions 140 to 319 in the Core/E1 region as shown in Figure 5;
- a sequence having a homology of more than 70%, preferably more than 72%, more preferably more than 75% homology, most preferably more than 81% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 (HD10, BR36, BR33 sequences) in the E1 region spanning positions 192 to 319 as shown in Figure 5;
- a sequence having a homology of more than 86%, preferably more than 88%, and most preferably more than 90% homology to the amino acid sequences as represented in SEQ ID NO 148 (type 3c); BE98 in the region spanning positions 1 to 110 in the Core region as shown in Figure 5;
- a sequence having a homology of more than 76%, preferably more than 78%, most preferably more than 80% to any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40 (HCCl53, HD10, BR36 sequences) in the region spanning positions 1646 to 1764 in the NS3/NS4 region as shown in Figure 7 and 11;
- a sequence having a homology of more than 81%, preferably more than 83%, and most preferably more than 86% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 (HD10, BR36, BR33 sequences) in the region spanning positions 140 to 319 in the Core/E1 region as shown in Figure 5;
- a sequence having a homology of more than 81.5%, preferably more than 83%, and most

preferably more than 86% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 (HD10, BR36, BR33 sequences) in the E1 region spanning positions 192 to 319 as shown in Figure 5;

- a sequence having a homology of more than 86%, preferably more than 88%, most preferably more than 90% to the amino acid sequence as represented in SEQ ID NO 150; (type 3c BE98) in the region spanning positions 2645 to 2757 in the NS5B region as shown in Figure 2.

According to yet another embodiment, the present invention relates to a composition as defined above, wherein said contiguous sequence is selected from any of the following HCV amino acid type 4 sequences:

- a sequence having a homology of more than 80%, preferably more than 82%, most preferably more than 84% homology to any of the amino acid sequences as represented in SEQ ID NO 118, 120, and 122 (GB358, GB549, GB809 sequences) in the region spanning positions 127 to 319 of the Core/E1 region as shown in Figure 5;
- a sequence having a homology of more than 73%, preferably more than 75%, most preferably more than 78% homology in the E1 region spanning positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO 118, 120, and 122 (GB358, GB549, GB809 sequences) in the region spanning positions 140 to 319 of the Core/E1 region as shown in Figure 5;
- a sequence having more than 85%, preferably more than 86%, most preferably more than 87% homology to any of the amino acid sequences as represented in SEQ ID NO 118, 120 or 122 (GB358, GB549, GB809 sequences) in the region spanning positions 192 to 319 of E1 as shown in Figure 5;
- a sequence showing more than 73%, preferably more than 74%, most preferably more than 75% homology to any of the amino acid sequences as represented in SEQ ID NO 106, 108, 110, 112, 114 or 116 (GB48, GB116, GB215, GB358, GB549, GB809 sequences) in the region spanning positions 2645 to 2757 of the NS5B region as shown in Figure 2;
- a sequence having any of the sequences as represented in SEQ ID NO 164 or 166 (GB809 and CAM600 sequences) in the Core/E1 region as shown in Figure 5;
- a sequence having any of the sequences as represented in SEQ ID NO 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188 or 190 (CAM600, GB809, CAMG22, CAMG27, GB549, GB438, CAR4/1205, CAR4/901, GB116, GB215, GB958, GB809-4 sequences) in the E1 region as shown in Figure 5;

a sequence having any of the sequences as represented in SEQ ID NO 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212 (GB358, GB724, BE100, PC, CAM600, CAMG22, etc.) in the NS5B region.

The above-mentioned type 4 peptides polypeptides comprise at least an amino acid sequence selected from any HCV type 4 polyprotein with the exception of core sequence as disclosed by Simmonds et al. (1993, EG-29, see Figure 5).

According to yet another aspect, the present invention relates to a composition as defined above, wherein said contiguous sequence is selected from any of the following HCV amino acid type 5 sequences:

- a sequence having more than 93%, preferably more than 94%, most preferably more than 95% homology in the region spanning Core positions 1 to 191 to any of the amino acid sequences as represented in SEQ ID NO 42, 44, 46, 48, 50, 52 or 54 (PC sequences) and SEQ ID NO 152 (BE95) as shown in Figure 5;
- a sequence having more than 73%, preferably more than 74%, most preferably more than 76% homology in the region spanning E1 positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO 42, 44, 46, 48, 50, 52 or 54 (PC sequences) as shown in Figure 5;
- a sequence having a more than 78%, preferably more than 80%, most preferably more than 83% homology to any of the amino acid sequences as represented in SEQ ID NO 42, 44, 46, 48, 50, 52, 54, 154, 156 (BE95, BE100) (PC sequences) in the region spanning positions 1 to 319 of the Core/E1 region as shown in Figure 5;
- a sequence having more than 90%, preferably more than 91%, most preferably more than 92% homology to any of the amino acid sequences represented in SEQ ID NO 56 to 58 (PC sequences) in the region spanning positions 1286 to 1403 of the NS3 region as shown in Figure 7 or 11;
- a sequence having more than 66%, more particularly 68%, most particularly 70% or more homology to any of the amino acid sequences as represented in SEQ ID NO 60 or 62 (PC sequences) in the region spanning positions 1646 to 1764 of the NS3/4 region as shown in Figure 7 or 11.

According to yet another embodiment, the present invention relates to a composition as defined above, wherein said contiguous sequence is selected from any of the following HCV amino acid type 2d sequences:

- a sequence having more than 83%, preferably more than 85%, most preferably more than

87% homology to the amino acid sequence as represented in SEQ ID NO 144 (NE92) in the region spanning positions 1 to 319 of the Core/E1 region as shown in Figure 5;

- a sequence having more than 79%, preferably more than 81%, most preferably more than 84% homology in the region spanning E1 positions 192 to 319 to the amino acid sequence as represented in SEQ ID NO 144 (NE92) as shown in Figure 12;
- a sequence having more than 95%, more particularly 96%, most particularly 97% or more homology to the amino acid sequence as represented in SEQ ID NO 146 (NE92) in the region spanning positions 2645 to 2757 of the NS5B region as shown in Figure 2.

The present invention also relates to a recombinant vector, particularly for cloning and/or expression, with said recombinant vector comprising a vector sequence, an appropriate prokaryotic, eukaryotic or viral promoter sequence followed by the nucleotide sequences as defined above, with said recombinant vector allowing the expression of any one of the HCV type 2 and/or HCV type 3 and/or type 4 and/or type 5 derived polypeptides as defined above in a prokaryotic, or eukaryotic host or in living mammals when injected as naked DNA, and more particularly a recombinant vector allowing the expression of any of the following HCV type 2d, type 3, type 4 or type 5 polypeptides spanning the following amino acid positions:

- a polypeptide starting at position 1 and ending at any position in the region between positions 70 and 326, more particularly a polypeptide spanning positions 1 to 70, 1 to 85, positions 1 to 120, positions 1 to 150, positions 1 to 191, positions 1 to 200, for expression of the Core protein, and a polypeptide spanning positions 1 to 263, positions 1 to 326, for expression of the Core and E1 protein;
- a polypeptide starting at any position in the region between positions 117 and 192, and ending at any position in the region between positions 263 and 326, for expression of E1, or forms that have the putative membrane anchor deleted (positions 264 to 293 plus or minus 8 amino acids);
- a polypeptide starting at any position in the region between positions 1556 and 1688, and ending at any position in the region between positions 1739 and 1764, for expression of the NS4 regions, more particularly a polypeptide starting at position 1658 and ending at position 1711 for expression of the NS4a antigen, and more particularly, a polypeptide starting at position 1712 and ending between positions 1743 and 1972, for example 1712-1743, 1712-1764, 1712-1782, 1712-1972, 1712 to 1782 and 1902 to 1972 for expression of the NS4b protein or parts thereof.

The term "vector" may comprise a plasmid, a cosmid, a phage, or a virus.

In order to carry out the expression of the polypeptides of the invention in bacteria such as E. coli or in eukaryotic cells such as in S. cerevisiae, or in cultured vertebrate or invertebrate hosts such as insect cells, Chinese Hamster Ovary (CHO), COS, BHK, and MDCK cells, the following steps are carried out:

transformation of an appropriate cellular host with a recombinant vector, in which a nucleotide sequence coding for one of the polypeptides of the invention has been inserted under the control of the appropriate regulatory elements, particularly a promoter recognized by the polymerases of the cellular host and, in the case of a prokaryotic host, an appropriate ribosome binding site (RBS), enabling the expression in said cellular host of said nucleotide sequence. In the case of an eukaryotic host any artificial signal sequence or pre/pro sequence might be provided, or the natural HCV signal sequence might be employed, e.g. for expression of E1 the signal sequence starting between amino acid positions 117 and 170 and ending at amino acid position 191 can be used, for expression of NS4, the signal sequence starting between amino acid positions 1646 and 1659 can be used, culture of said transformed cellular host-under conditions enabling the expression of said insert.

The present invention also relates to a composition as defined above, wherein said polypeptide is a recombinant polypeptide expressed by means of an expression vector as defined above.

The present invention also relates to a composition as defined above, for use in a method for immunizing a mammal, preferably humans, against HCV comprising administring a sufficient amount of the composition possibly accompanied by pharmaceutically acceptable adjuvants, to produce an immune response, more particularly a vaccine composition including HCV type 3 polypeptides derived from the Core, E1 or the NS4 region and/or HCV type 4 and/or HCV type 5 polypeptides and/or HCV type 2d polypeptides.

The present invention also relates to an antibody raised upon immunization with a composition as defined above by means of a process as defined above, with said antibody being reactive with any of the polypeptides as defined above, and with said antibody being preferably a monoclonal antibody.

The monoclonal antibodies of the invention can be produced by any hybridoma liable to be formed according to classical methods from splenic cells of an animal, particularly from

a mouse or rat, immunized against the HCV polypeptides according to the invention, or muteins thereof, or fragments thereof as defined above on the one hand, and of cells of a myeloma cell line on the other hand, and to be selected by the ability of the hybridoma to produce the monoclonal antibodies recognizing the polypeptides which has been initially used for the immunization of the animals.

The antibodies involved in the invention can be labelled by an appropriate label of the enzymatic, fluorescent, or radioactive type.

The monoclonal antibodies according to this preferred embodiment of the invention may be humanized versions of mouse monoclonal antibodies made by means of recombinant DNA technology, departing from parts of mouse and/or human genomic DNA sequences coding for H and L chains or from cDNA clones coding for H and L chains.

Alternatively the monoclonal antibodies according to this preferred embodiment of the invention may be human monoclonal antibodies. These antibodies according to the present embodiment of the invention can also be derived from human peripheral blood lymphocytes of patients infected with type 3, type 4 or type 5 HCV, or vaccinated against HCV. Such human monoclonal antibodies are prepared, for instance, by means of human peripheral blood lymphocytes (PBL) repopulation of severe combined immune deficiency (SCID) mice (for recent review, see Duchosal et al. 1992).

The invention also relates to the use of the proteins of the invention, muteins thereof, or peptides derived therefrom for the selection of recombinant antibodies by the process of repertoire cloning (Persson et al., 1991).

Antibodies directed to peptides derived from a certaing genotype may be used either for the detection of such HCV genotypes, or as therapeutic agents.

The present invention also relates to the use of a composition as defined above for incorporation into an immunoassay for detecting HCV, present in biological sample liable to contain it, comprising at least the following steps:

- (i) contacting the biological sample to be analyzed for the presence of HCV antibodies with any of the compositions as defined above preferably in an immobilized form under appropriate conditions which allow the formation of an immune complex, wherein said polypeptide can be a biotinylated polypeptide which is covalently bound to a solid substrate by means of streptavidin or avidin complexes,
- (ii) removing unbound components,
- (iii) incubating the immune complexes formed with heterologous antibodies, which

specifically bind to the antibodies present in the sample to be analyzed, with said heterologous antibodies having conjugated to a detectable label under appropriate conditions.

(iv) detecting the presence of said immunecomplexes visually or by means of densitometry and inferring the HCV serotype present from the observed hybridization pattern.

The present invention also relates to the use of a composition as defined above, for incorporation into a serotyping assay for detecting one or more serological types of HCV present in a biological sample liable to contain it, more particularly for detecting E1 and NS4 antigens or antibodies of the different types to be detected combined in one assay format, comprising at least the following steps:

- (i) contacting the biological sample to be analyzed for the presence of HCV antibodies or antigens of one or more serological types, with at least one of the compositions as defined above, an immobilized form under appropriate conditions which allow the formation of an immunecomplex,
- (ii) removing unbound components,
- (iii) incubating the immunecomplexes formed with heterologous antibodies, which specifically bind to the antibodies present in the sample to be analyzed, with said heterologous antibodies having conjugated to a detectable label under appropriate conditions,
- (iv) detecting the presence of said immunecomplexes visually or by means of densitometry and inferring the presence of one or more HCV serological types present from the observed binding pattern.

The present invention also relates to the use of a composition as defined above, for immobilization on a solid substrate and incorporation into a reversed phase hybridization assay, preferably for immobilization as parallel lines onto a solid support such as a membrane strip, for determining the presence or the genotype of HCV according to a method as defined above.

The present invention thus also relates to a kit for determining the presence of HCV genotypes as defined above present in a biological sample liable to contain them, comprising:

possibly at least one primer composition containing any primer selected from those defined above or any other HCV type 3 and/or HCV type 4, and/or HCV type 5, or universal HCV primers,

- at least one probe composition as defined above, with said probes being preferentially immobilized on a solid substrate, and more preferentially on one and the same membrane strip,
- a buffer or components necessary for producing the buffer enabling hybridization
   reaction between these probes and the possibly amplified products to be carried out,
- means for detecting the hybrids resulting from the preceding hybriziation,
- possibly also including an automated scanning and interpretation device for inferring the HCV genotypes present in the sample from the observed hybridization pattern.

The genotype may also be detected by means of a type-specific antibody as defined above, which is linked to any polynucleotide sequence that can afterwards be amplified by PCR to detect the immune complex formed (Immuno-PCR, Sano et al., 1992);

The present invention also relates to a kit for determining the presence of HCV antibodies as defined above present in a biological sample liable to contain them, comprising:

- at least one polypeptide composition as defined above, preferentially in combination with other polypeptides or peptides from HCV type 1, HCV type 2 or other types of HCV, with said polypeptides being preferentially immobilized on a solid substrate, and more preferentially on one and the same membrane strip,
- a buffer or components necessary for producing the buffer enabling binding reaction between these polypeptides and the antibodies against HCV present in the biological sample,
- means for detecting the immunecomplexes formed in the preceding binding reaction,
- possibly also including an automated scanning and interpretation device for inferring the HCV genotypes present in the sample from the observed binding pattern.

#### Figure Legends

#### Figure 1

Alignment of consensus nucleotide sequences for each of the type 3a isolates BR34, BR36, and BR33, deduced from the clones with SEQ ID NO 1, 5, 9; type 4 isolates GB48, GB116, GB215, GB358, GB549, GB809, CAM600, CAMG22, GB438, CAR4/1205, CAR1/501 (SEQ ID NO. 106, 108, 110, 112, 114, 116, 201, 203, 205, 207, 209 and 211); type 5a isolates BE95 and BE96 (SEQ ID NO 159 and 161) and type 2d isolate NE92 (SEQ ID NO 145) from the region between nucleotides 7932 and 8271, with known sequences from the corresponding region of isolates HCV-1, HCV-J, HC-J6, HC-J8, T1 and T9, and others as shown in Table 3.

#### Figure 2

Alignment of amino acids sequences deduced from the nucleic acid sequences as represented in Figure 1 from the subtype 3a clones BR34 (SEQ ID NO 2, 4), BR36 (SEQ ID NO 6, 8) and BR33 (SEQ ID NO 10, 12), the subtype 3c clone BE98 (SEQ ID NO 150), and the type 4 clones GB48 (SEQ ID NO 107), GB116 (SEQ ID NO 109), GB215 (SEQ ID NO 111), GB358 (SEQ ID NO 113), GB549 (SEQ ID NO 115) GB809 (SEQ ID NO 117); CAM600, CAMG22, GB438, CAR4/1205, CAR1/501 (SEQ ID NO 202, 204, 206, 208, 210, 212); the type 5a clones BE95 and BE96 (SEQ ID NO 160 and 162); as well as the subtype 2d isolate NE92 (SEQ ID NO 146) from the region between amino acids 2645 to 2757 with known sequences from the corresponding region of isolates HCV-I, HCV-J, HC-J6, and HC-J8, T1 and T9, and other sequences as shown in Table 3.

#### Figure 3

Alignment of type 2d, 3c, 4 and 5a nucleotide sequences from isolates NE92, BE98, GB358, GB809, CAM600, GB724, BE95 (SEQ ID NO 143, 147, 191, 163, 165, 193 and 151) in the Core region between nucleotide positions 1 and 500, with known sequences from the corresponding region of type 1, type 2, type 3 and type 4 sequences.

#### Figure 4

Alignment of nucleotide sequences for the subtype 2d isolate NE92 (SEQ ID NO 143), the type 4 isolates GB358 (SEQ ID NO 118 and 187), GB549 (SEQ ID NO 120 and 175), and

GB809-2 (SEQ ID NO 122 and 169), GB 809-4, BG116, GB215, CAM600, CAMG22, CAMG27, GB438, CAR4/1205, CAR4/901 (SEQ ID NO 189, 183, 185, 167, 171, 173, 177, 179, 181), sequences for each of the subtype 3a isolates HD10, BR36, and BR33, (SEQ ID NO 13, 15, 17 (HD10), 19, 21 (BR36) and 23, 25 or 27 (BR23) and the subtype 5a isolates BE95 and BE100 (SEQ ID NO 143 and 195) from the region between nucleotides 379 and 957, with known sequences from the corresponding region of type 1 and 2 and 3.

#### Figure 5

Alignment of amino acid sequences deduced from the new HCV nucleotide sequences of the Core/E1 region of isolates BR33, BR36, HD10, GB358, GB549, and GB809, PC or BE95, CAM600, and GB724 (SEQ ID NO. 14, 20, 24, 119 or 192, 121, 123 or 164, 54 or 152, 166 and 194) from the region between positions 1 and 319, with known sequences from type 1a (HCV-1), type 1b (HCV-J), type 2a (HC-JG), type 2b (HC-J8), NZL1, HCV-TR, positions 7-89 of type 3a (E-b1), and positions 8-88 of type 4a (EG-29). V-Core, variable region with type-specific features in the core protein, V1, variable region 1 of the E1 protein, V2, variable region 2 of the E1 protein, V3, variable region 3 of the E1 protein, V4, variable region 4 of the E1 protein, V5, variable region 5 of the E1 protein.

#### Figure 6

Alignment of nucleotide sequences of isolates HCCL53, HD10 and BR36, deduced from clones with SEQ ID NO 29, 31, 33, 35, 37 and 39, from the NS3/4 region between nucleotides 4664 to 5292, with known sequences from the corresponding region of isolates HCV-1, HCV-J, HC-J6, and HC-J8, EB1, EB2, EB6 and EB7.

#### Figure 7

Alignment of amino acid sequences deduced from the new HCV nucleotide sequences of the NS3/NS4 region of isolate BR36 (SEQ ID NO 36, 38 and 40) and BE95 (SEQ ID NO 270). NS4-1, indicates the region that was synthesized as synthetic peptide 1 of the NS4 region, NS4-5, indicates the region that was synthesized as synthetic peptide 5 of the NS4 region; NS4-7, indicates the region that was synthesized as synthetic peptide 7 of the NS4 region.

#### Figure 8

Reactivity of the three LIPA-selected (Stuyver et al., 1993) type 3 sera on the Inno-LIA HCV Ab II assay (Innogenetics) (left), and on the NS4-LIA test. For the NS4-LIA test, NS4-1, NS4-5, and NS4-7 peptides were synthesized based on the type 1 (HCV-1), type 2 (HC-J6) and type 3 (BR36) prototype isolate sequences as shown in Table 4, and applied as parallel lines onto a membrane strip as indicated. 1, serum BR33, 2, serum HD10, 3, serum DKH.

#### Figure 9

Nucleotide sequences of Core/E1 clones obtained from the PCR fragments PC-2, PC-3, and PC-4, obtained from serum BE95 (PC-2-1 (SEQ ID NO 41), PC-2-6 (SEQ ID NO 43), PC-4-1 (SEQ ID NO 45), PC-4-6 (SEQ ID NO 47), PC-3-4 (SEQ ID NO 49), and PC-3-8 (SEQ ID NO 51)) of subtype 5a isolate BE95.

A consensus sequence is shown for the Core and E1 region of isolate BE95, presented as PC C/E1 with SEQ ID NO 53. Y, C or T, R, A or G, S, C or G.

## Figure 10

Alignment of nucleotide sequences of clones with SEQ ID NO 197 and 199 (PC sequences, see also SEQ ID NO 55, 57, 59) and SEQ ID NO 35, 37 and 39 (BR36 sequences) from the NS3/4 region between nucleotides 3856 to 5292, with known sequences from the corresponding region of isolates HCV-1, HCV-J, HC-J6, and HC-J8.

#### Figure 11

Alignment of amino acid sequences of subtype 5a BE95 isolate PC clones with SEQ ID NO 56 and 58, from the NS3/4 region between amino acids 1286 to 1764, with known sequences from the corresponding region of isolates HCV-1, HCV-J, HC-J6, and HC-J8.

#### Figure 12

Alignment of amino acid sequences of subtype 5a isolate BE95 (SEQ ID NO 158) in the E1/E2 region spanning positions 328 to 546, with known sequences from the corresponding region of isolates HCV-1, HCV-J, HC-J6, HC-J8, NZL1 and HCV-TR (see Table 3).

#### Figure 13

Alignment of the nucleotide sequences of subtype 5a isolate BE95 (SEQ ID NO 157) in the E1/E2 region with known HCV sequences as shown in Table 3.

#### **EXAMPLES**

#### Example 1: The NS5b region of HCV type 3

Type 3 sera, selected by means of the INNO-LiPA HCV research kit (Stuyver et al., 1993) from a number of Brazilian blood donors, were positive in the HCV antibody ELISA (Innotest HCV Ab II; Innogenetics) and/or in the INNO-LIA HCV Ab II confirmation test (Innogenetics). Only those sera that were positive after the first round of PCR reactions (Stuyver et al., 1993) were retained for further study.

Reverse transcription and nested PCR: RNA was extracted from 50  $\mu$ l serum and subjected to cDNA synthesis as described (Stuyver et al., 1993). This cDNA was used as template for PCR, for which the total volume was increased to 50  $\mu$ l containing 10 pmoles of each primer, 3  $\mu$ l of 10x Pfu buffer 2 (Stratagene) and 2.5 U of Pfu DNA polymerase (Stratagene). The cDNA was amplified over 45 cycles consisting of 1 min 94°C, 1 min 50°C and 2 min 72°C. The amplified products were separated by electrophoresis, isolated, cloned and sequenced as described (Stuyver et al., 1993).

Type 3a and 3b-specific primers in the NS5 region were selected from the published sequences (Mori et al., 1992) as follows:

for type 3a:

HCPr161(+): 5'-ACCGGAGGCCAGGAGAGTGATCTCCTCC-3' (SEQ ID NO 63) and HCPr162(-): 5'-GGGCTGCTCTATCCTCATCGACGCCATC-3' (SEQ ID NO 64);

for type 3b:

HCPr163(+): 5'-GCCAGAGGCTCGGAAGGCGATCAGCGCT-3' (SEQ ID O 65) and HCPr164(-): 5'-GAGCTGCTCTGTCCTCCTCGACGCCGCA-3' (SEQ ID NO 66)

Using the Line Probe Assay (LiPA) (Stuyver et al., 1993), seven high-titer type 3 sera were selected and subsequently analyzed with the primer sets HCPr161/162 for type 3a, and HCPr163/164 for type 3b. None of these sera was positive with the type 3b primers. NS5 PCR fragments obtained using the type 3a primers from serum BR36 (BR36-23), serum BR33 (BR33-2) and serum BR34 (BR34-4) were selected for cloning. The following sequences were obtained from the PCR fragments:

From fragment BR34-4:

BR34-4-20 (SEQ ID NO 1), BR34-4-19 (SEQ ID NO 3)

From fragment BR36-23:

BR36-23-18 (SEQ ID NO 5), BR36-23-20 (SEQ ID NO 7)

From fragment BR33-2:

BR33-2-17 (SEQ ID NO 9), BR33-2-21 (SEQ ID NO 11)

An alignment of sequences with SEQ ID NO 1, 5 and 9 with known sequences is given in Figure 1. An alignment of the deduced amino acid sequences is shown in Figure 2. The 3 isolates are very closely related to each other (mutual homologies of about 95%) and to the published sequences of type 3a (Mori et al., 1992), but are only distantly related to type 1 and type 2 sequences (Table 5). Therefore, it is clearly demonstrated that NS5 sequences from LiPA-selected type 3 sera are indeed derived from a type 3 genome. Moreover, by analyzing the NS5 region of serum BR34, for which no 5'UR sequences were determined as described in Stuyver et al. (1993), the excellent correlation between typing by means of the LiPA and genotyping as deduced from nucleotide sequencing was further proven.

## Example 2: The Core/E1 region of HCV type 3

After aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J (Kato et al., 1990), HC-J6 (Okamoto et al., 1991), and HC-J8 (Okamoto et al., 1992), PCR primers were chosen those regions of little sequence variation. **Primers** HCPr23(+): CTCATGGGGTACATTCCGCT-3' (SEQ ID NO 67) and HCPr54(-): 5'-TATTACCAGTTCATCATCATATCCCA-3' (SEQ ID NO 68), were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems). This set of primers was selected to amplify the sequence from nucleotide 397 to 957 encoding amino acids 140 to 319 (Kato et al., 1990): 52 amino acids from the carboxyterminus of core and 128 amino acids of E1 (Kato et al., 1990). The amplification products BR36-9, BRR33-1, and HD10-2 were cloned as described (Stuyver et al., 1993). The following clones were obtained from the PCR fragments:

From fragment HD10-2:

HD10-2-5 (SEQ ID NO 13), HD10-2-14 (SEQ ID NO 15), HD10-2-21 (SEQ ID NO 17) From fragment BR36-9:

BR36-9-13 (SEQ ID NO 19), BR36-9-20 (SEQ ID NO 21),

From fragment BR33-1:

BR33-1-10 (SEQ ID NO 23), BR33-1-19 (SEQ ID NO 25), BR33-1-20 (SEQ ID NO 27), An alignment of the type 3 E1 nucleotide sequences (HD10, BR36, BR33) with SEQ ID NO 13, 19 and 23 with known E1 sequences is presented in Figure 4. Four variations were detected in the E1 clones from serum HD10 and BR36, while only 2 were found in BR33. All are silent third letter variations, with the exception of mutations at position 40 (L to P)

and 125 (M to I). The homologies of the type 3 E1 region (without core) with type 1 and 2 prototype sequences are depicted in Table 5.

In total, 8 clones covering the core/E1 region of 3 different isolates were sequenced and the E1 portion was compared with the known genotypes (Table 3) as shown in Figure 5. After computer analysis of the deduced amino acid sequence, a signal-anchor sequence at the core carboxyterminus was detected which might, through analogy with type 1b (Hijikata et al., 1991), promote cleavage before the LEWRN sequence (position 192, Fig. 5). The L-to-P mutation in one of the HD10-2 clones resides in this signal-anchor region and potentially impairs recognition by signal peptidase (computer prediction). Since no examples of such substitutions were found at this position in previously described sequences, this mutation might have resulted from reverse transcriptase or Pfu polymerase misincorporation. The 4 amino-terminal potential N-linked glycosylation sites, which are also present in HCV types la and 2, remain conserved in type 3. The N-glycosylation site in type 1b (aa 250, Kato et al., 1990) remains a unique feature of this subtype. All E1 cysteines, and the putative transmembrane region (aa 264 to 293, computer prediction) containing the aspartic acid at position 279, are conserved in all three HCV types. The following hypervariable regions can be delineated: V1 from aa 192 to 203 (numbering according to Kato et al., 1990), V2 (213-223), V3 (230-242), V4 (248-257), and V5 (294-303). Such hydrophilic regions are thought to be exposed to the host defense mechanisms. This variability might therefore have been induced by the host's immune response. Additional putative N-linked glycosylation sites in the V4 region in all type 1b isolates known today and in the V5 region of HC-J8 (type 2b) possibly further contribute to modulation of the immune response. Therefore, analysis of this region, in the present invention, for type 3 and 4 sequences has been instrumental in the delineation of epitopes that reside in the V-regions of E1, which will be critical for future vaccine and diagnostics development.

# Example 3: The NS3/NS4 region of HCV Type 3

For the NS3/NS4 border region, the following sets of primers were selected in the regions of little sequence variability after aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J (Kato et al., 1990), HC-J6 (Okamoto et al., 1991), and HC-J8 (Okamoto et al., 1992) (smaller case lettering is used for nucleotides added for cloning purposes):

set A:

HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 69)

- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set B:
- HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 69)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQ ID NO 71) set C:
- HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set D:
- HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set E:
- HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 69)
- HCPr119(-): actagtcgactaRTTIGCIATIAGCCG/TRTTCATCCAYTG-3' (SEQID NO 73) set F:
- HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)
- HCPr119(-): actagtcgactaRTTIGCIATIAGCCG/TRTTCATCCAYTG-3' (SEQ ID NO 73) set G:
- HCPr131(+): 5'-ggaattctagaCCITCITGGGAYGARAYITGGAARTG-3' (SEQ ID NO 74)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set H:
- HCPr130(+): 5'-ggaattctagACIGCITAYCARGCIACIGTTTGYGC-3' (SEQ ID NO 75)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set I:
- HCPr134(+): 5'-CATATAGATGCCCACTTCCTATC-3' (SEQ ID NO 76)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set J:
- HCPr131(+): 5'-ggaattctagaCCITCITGGGAYGARAYITGGAARTG-3' (SEQ ID NO 74)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQ ID NO 71)

set K:

HCPr130(+): 5'-ggaattctagACIGCITAYCARGCIACIGTITGYGC-3' (SEQ ID NO 75)
HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQ ID NO 71)

set L:

HCPr134(+): 5'-CATATAGATGCCCACTTCCTATC-3' (SEQ ID NO 76)

HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set M:

HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and

HCPr4(-): 5'-GACATGCATGTCATGATGTA-3 (SEQ ID NO 78)

set N:

HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and

HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set O:

HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and

HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70)

No PCR products could be obtained with the sets of primers A, B, C, D, E, F, G, H, I, J, K, L, M, and N, on random-primed cDNA obtained from type 3 sera. With the primer set O, no fragment could be amplified from type 3 sera. However, a smear containing a few weakly stainable bands was obtained from serum BR36. After sequence analysis of several DNA fragments, purified and cloned from the area around 300 bp on the agarose gel, only one clone, HCCl53 (SEQ ID NO 29), was shown to contain HCV information. This sequence was used to design primer HCPr152.

A new primer set P was subsequently tested on several sera.

set P:

HCPr152(+): 5'-TACGCCTCTTCTATATCGGTTGGGGCCTG-3' (SEQ ID NO 79) and HCPr66(-): 5'-CTATTATTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70)

The 464-bp HCPr152/66 fragment was obtained from serum BR36 (BR36-20) and serum HD10 (HD10-1). The following clones were obtained from these PCR products:

From fragment HD10-1:

HD10-1-25 (SEQ ID NO 31), HD10-1-3 (SEQ ID NO 33),

From fragment BR36-20:

BR36-20-164 (SEQ ID NO 35), BR36-20-165 (SEQ ID NO 37), BR36-20-166 (SEQ ID NO 39),

The nucleotide sequences obtained from clones with SEQ ID NO 29, 31, 33, 35, 37 or 39 are shown aligned with the sequences of prototype isolates of other types of HCV in Figure 6. In addition to one silent 3rd letter variation, one 2nd letter mutation resulted in an

E to G substitution at position 175 of the deduced amino acid sequence of BR36 (Fig. 7). Serum HD10 clones were completely identical. The two type 3 isolates were nearly 94% homologous in this NS4 region. The homologies with other types are presented in Table 5.

## Example 4: Analysis of the anti-NS4 response to type-specific peptides

As the NS4 sequence contains the information for an important epitope cluster, and since antibodies towards this region seem to exhibit little cross-reactivity (Chan et al., 1991), it was worthwhile to investigate the type-specific antibody response to this region. For each of the 3 genotypes, HCV-1 (Choo et al., 1991), HC-J6 (Okamoto et al., 1991) and BR36 (present invention), three 20-mer peptides were synthesized covering the epitope region between amino acids 1688 and 1743 (as depicted in table 6). The synthetic peptides were applied as parallel lines onto membrane strips. Detection of anti-NS4 antibodies and color development was performed according to the procedure described for the INNO-LIA HCV Ab II kit (Innogenetics, Antwerp). Peptide synthesis was carried out on a 9050 PepSynthesizer (Millipore). After incubation with 15 LiPA-selected type 3 sera, 9 samples showed reactivity towards NS4 peptides of at least 2 different types, but a clearly positive reaction was observed for 3 sera (serum BR33, HD30 and DKH) on the type 3 peptides, while negative (serum BR33 and HD30) or indeterminate (serum DKH) on the type 1 and type 2 NS4 peptides; 3 sera tested negative for anti-NS4 antibodies (Figure 8). Using the same membrane strips coated with the 9 peptides as indicated above and as shown in Figure 8, 38 type 1 sera (10 type 1a and 28 type 1b), 11 type 2 sera (10 type 2a and 1 type 2b), 12 type 3a sera and 2 type 4 sera (as determined by the LiPA procedure) were also tested. As shown in Table 8, the sera reacted in a genotype-specific manner with the NS4 epitopes. These results demonstrate that type-specific anti-NS4 antibodies can be detected in the sera of some patients. Such genotype-specific synthetic peptides might be employed to develop serotyping assays, for example a mixture of the nine peptides as indicated above, or combined with the NS4 peptides from the HCV type 4 or 6 genotype or from new genotypes corresponding to the region between amino acids 1688 and 1743, or synthetic peptides of the NS4 region between amino acids 1688 and 1743 of at least one of the 6 genotypes, combined with the E1 protein or deletion mutants thereof, or synthetic E1 peptides of at least one of the genotypes. Such compositions could be further extended with type-specific peptides or proteins, including for example the region between amino acids 68 and 91 of the core protein, or more preferably the region between amino acids 68 and 78. Furthermore, such type-specific

antigens may be advantageously used to improve current diagnostic screening and confirmation assays and/or HCV vaccines.

## Example 5 The Core and E1 regions of HCV type 5

Sample BE95 was selected from a group of sera that reacted positive in a prototype Line Probe Assay as described earlier (Stuyver et al., 1993), because a high-titer of HCV RNA could be detected, enabling cloning of fragments by a single round of PCR. As no sequences from any coding region of type 5 has been disclosed yet, synthetic oligonucleotides for PCR amplification were chosen in the regions of little sequence variation after aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J (Kato et al., 1990), HC-J6 (Okamoto et al., 1991), HC-J8 (Okamoto et al., 1992), and the new type 3 sequences of the present invention HD10, BR33, and BR36 (see Figure 5, Example 2). The following sets of primers were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems):

Set 1:

HCPr52(+): 5'-atgTTGGGTAAGGTCATCGATACCCT-3' (SEQ ID NO 80) and

HCPr54(-): 5'-ctattaCCAGTTCATCATCATATCCCA-3' (SEQ ID NO 78)

Set 2:

HCPr41(+): 5'-CCCGGGAGGTCTCGTAGACCGTGCA-3' (SEQ ID NO 81) and

HCPr40(-): 5'-ctattaAAGATAGAGAAAGAGCAACCGGG-3'(SEQ ID NO 82)

Set 3:

HCPr41(+): 5'-CCCGGGAGGTCTCGTAGACCGTGCA-3' (SEQ ID NO 81) and

HCPr54(-): 5'-ccattaCCAGTTCATCATCATATCCCA-3' (SEQ ID NO 78)

The three sets of primers were employed to amplify the regions of the type 5 isolate PC as described (Stuyver et al., 1993). Set 1 was used to amplify the E1 region and yielded fragment PC-4, set 2 was designed to yield the Core region and yielded fragment PC-2. Set 3 was used to amplify the Core and E1 region and yielded fragment PC-3. These fragments were cloned as described (Stuyver et al., 1993). The following clones were obtained from the PCR fragments:

From fragment PC-2:

PC-2-1 (SEQ ID NO 41), PC-2-6 (SEQ ID NO 43),

From fragment PC-4:

PC-4-1 (SEQ ID NO 45), PC-4-6 (SEQ ID NO 47),

From fragment PC-3:

PC-3-4 (SEQ ID NO 49), PC-3-8 (SEQ ID NO 51)

An alignment of sequences with SEQ ID NO 41, 43, 45, 47, 49 and 51, is given in Figure 9. A consensus amino acid sequence (PC C/E1; SEQ ID NO 54) can be deduced from each of the 2 clones cloned from each of the three PCR fragments as depicted in Figure 5, which overlaps the region between nucleotides 1 and 957 (Kato et al., 1990). The 6 clones are very closely related to each other (mutual homologies of about 99.7%).

An alignment of nucleotide sequence with SEQ ID NO 53 or 151 (PC C/E1 from isolate BE95) with known nucleotide sequences from the Core/E1 region is given in Figure 3. The clone is only distantly related to type 1, type 2, type 3 and type 4 sequences (Table 5).

# Example 6: NS3/NS4 region of HCV type 5

Attempts were undertaken to clone the NS3/NS4 region of the isolate BE95, described in example 5. The following sets of primers were selected in the regions of little sequence variability after aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J (Kato et al., 1991), HC-J6 (Okamoto et al., 1991), and HC-J8 (Okamoto et al., 1992) and of the sequences obtained from type 3 sera of the present invention (SEQ ID NO 31, 33, 35, 37 and 39); smaller case lettering is used for nucleotides added for cloning purposes:

set A:

HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 66)

HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set B:

HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 69)

HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQ ID NO 71) set C:

HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)

HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set D:

HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)

HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set E:

HCPr116(+): 5'-ttttAAATACATCATGRCITGYATG-3' (SEQ ID NO 69)

HCPr119(-): actagtcgactaRTTIGCIATIAGCCG/TRTTCATCCAYTG-3' (SEQ ID NO 73)

set F:

- HCPr117(+): 5'-ttttAAATACATCGCIRCITGCATGCA-3' (SEQ ID NO 72)
- HCPr119(-): actagtcgactaRTTIGCIATIAGCCG/TRTTCATCCAYTG-3' (SEQ ID NO 73) set G:
- HCPr131(+): 5'-ggaattctagaCCITCITGGGAYGARAYITGGAARTG-3' (SEQ ID NO 74)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set H:
- HCPr130(+): 5'-ggaattctagACIGCITAYCARGCIACIGTITGYGC-3' (SEQ ID NO 75)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set I:
- HCPr134(+): 5'-CATATAGATGCCCACTTCCTATC-3' (SEQ ID NO 76)
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70) set J:
- HCPr131(+): 5'-ggaattctagaCCITCITGGGAYGARAYITGGAARTG-3' (SEQ ID 74)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set K:
- HCPr130(+): 5'-ggaattctagACIGCITAYCARGCIACIGTITGYGC-3' (SEQ ID NO 75)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO 71) set L:
- HCPr134(+): 5'-CATATAGATGCCCACTTCCTATC-3' (SEQ ID NO 76)
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQID NO71) set M:
- HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and
- HCPr4(-): 5'-GACATGCATGTCATGATGTA-3' (SEQ ID NO 78) set N:
- HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and
- HCPr118(-): 5'-actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3' (SEQ ID NO 71)

set O:

- HCPr3(+): 5'-GTGTGCCAGGACCATC-3' (SEQ ID NO 77) and
- HCPr66 (-): 5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3' (SEQ ID NO 70)
  - No PCR products could be obtained with the sets of primers A, B, C, D, E, F, G,
- H, I, J, K, L, M, and N, on random-primed cDNA obtained from type 3 sera. However,

set O yielded what appeared to be a PCR artifact fragment estimated about 1450 base pairs, instead of the expected 628 base pairs. Although it is not expected that PCR artifact fragments contain information of the gene or genome that was targetted in the experiment, efforts were put in cloning of this artifact fragment, which was designated fragment PC-1. The following clones, were obtained from fragment PC-1:

PC-1-37 (SEQ ID NO 59 and SEQ ID NO 55), PC-1-48 (SEQ ID NO 61 and SEQ ID NO 57)

The sequences obtained from the 5' and 3' ends of the clones are given in SEQ ID NOS 55, 57, 59, and 61, and the complete sequences with SEQ ID NO 197 and 199 are shown aligned with the sequences of prototype isolates of other types of HCV in Figure 10 and the alignment of the deduced amino acid sequences is shown in Figure 11 and 7. Surprisingly, the PCR artifact clone contained HCV information. The positions of the sequences within the HCV genome are compatible with a contiguous HCV sequence of 1437 nucleotides, which was the estimated size of the cloned PCR artifact fragment. Primer HCPr66 primed correctly at the expected position in the HCV genome. Therefore, primer HCPr3 must have incidentally misprimed at a position 809 nucleotides upstream of its legitimate position in the HCV genome. This could not be expected since no sequence information was available from a coding region of type 5.

## Example 7: The E2 region of HCV type 5

Serum BE95 was chosen for experiments aimed at amplifying a part of the E2 region of HCV type 5.

After aligning the sequences of HCV-1 (2), HCV-J(1), HC-J6 (3), and HC-J8 (4), PCR primers were chosen in those regions of little sequence variation.

Primers HCPr109(+): 5'-TGGGATATGATGATGATGATGTC-3' (SEQ ID NO 141) and HCPr14(-): 5'-CCAGGTACAACCGAACCAATTGCC-3' (SEQ ID NO 142) were combined to amplify the aminoterminal region of the E2/NS1 region, and were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems). With primers HCPr109 and HCPr14, a PCR fragment of 661 bp was generated, containing 169 nucleodtides corresponding to the E1 carboxyterminus and 492 bases from the region encoding the E2 aminoterminus.

An alignment of the type 5 E1/E2 sequences with seq ID NO. 158 with known sequences is presented in Figure 10. The deduced protein sequence was compared with the different

genotypes (Fig. 12, amino acids 328-546). In the E1 region, there were no extra structural important motifs found. The aminoterminal part of E2 was hypervariable when compared with the other genotypes. All 6 N-glycosylation sites and all 7 cysteine residue's were conserved in this E2 region. To preserve alignment, it was necessary to introduce a gap between aa 474 and 475 as for type 3a, but not between aa 480 and 481, as for type 2.

#### Example 8: The NS5b region of HCV type 4

Type 4 sera GB48, GB116, GB215, and GB358, selected by means of the line probe assay (LiPA, Stuyver et al., 1993), as well as sera GB549 and GB809 that could not be typed by means of this LiPA (only hybridization was observed with the universal probes), were selected from Gabonese patients. All these sera were positive after the first round of PCR reactions for the 5' untranslated region (Stuyver et al., 1993) and were retained for further study.

RNA was isolated from the sera and cDNA synthesized as described in example 1.

Universal primers in the NS5 region were selected after alignment of the published sequences as follows:

HCPr206(+): 5'-TGGGGATCCCGTATGATACCCGCTGCTTTGA-3'

(SEQ ID NO. 124) and

HCPr207(-): 5'-GGCGGAATTCCTGGTCATAGCCTCCGTGAA-3'

(SEQ ID NO. 125);

and were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems). Using the Line Probe Assay (LiPA), four high-titer type 4 sera and 2 sera that could not be classified were selected and subsequently analyzed with the primer set HCPr206/207. NS5 PCR fragments obtained using these primers from serum GB48 (GB48-3), serum GB116 (GB116-3), serum GB215 (GB215-3), serum GB358 (GB358-3), serum GB549 (GB549-3), and serum GB809 (GB809-3), were selected for cloning. The following sequences were obtained from the PCR fragments:

From fragment GB48-3: GB48-3-10 (SEQ ID NO. 106)

From fragment GB116-3: GB116-3-5 (SEQ ID NO. 108)

From fragment GB215-3: GB215-3-8 (SEQ ID NO. 110)

From fragment GB358-3: GB358-3-3 (SEQ ID NO. 112)

From fragment GB549-3: GB549-3-6 (SEQ ID NO. 114)

From fragment GB809-3: GB809-3-1 (SEQ ID NO. 116)

An alignment of nucleotide sequences with SEQ ID NO. 106, 108, 110, 112, 114, and 116 with known sequences is given in Figure 1. An alignment of deduced amino acid sequences with SEQ ID NO. 107, 109, 111, 113, 115, and 117 with known sequences is given in Figure 2. The 4 isolates that had been typed as type 4 by means of LiPA are very closely related to each other (mutual homologies of about 95%), but are only distantly related to type 1, type 2, and type 3 sequences (e.g. GB358 shows homologies of 65.6 to 67.7% with other genotypes, Table 4). The sequence obtained from sera GB549 and GB809 also show similar homologies with genotypes 1, 2, and 3 (65.9 to 68.8% for GB549 and 65.0 to 68.5% for GB809, Table 4), but an intermediate homology of 79.7 to 86.8% (often observed between subtypes of the same type) exists between GB549 or GB809 with the group of isolates consisting of GB48, GB116, GB215, and GB358, or between GB549 and GB809. These data indicate the discovery of 3 new subtypes within the HCV genotype 4: in the present invention, these 3 subtypes are designated subtype 4c, represented by isolates GB48, GB116, GB215, and GB358, subtype 4g, represented by isolate GB549, and subtype 4e, represented by isolate GB809. Although the homologies observed between subtypes in the NS5 region seem to indicate a closer relationship between subtypes 4c and 4e, the homologies observed in the E1 region indicate that subtypes 4g and 4e show the closest relation (see example 8).

## Example 9: The Core/E1 region of HCV type 4

From each of the 3 new type 4 subtypes, one representative serum was selected for cloning experiments in the Core/E1 region. GB549 (subtype 4g) and GB809 (subtype 4e) were analyzed together with isolate GB358 that was chosen from the subtype 4c group.

Synthetic oligonucleotides:

After aligning the sequences of HCV-1 (2), HCV-J(1), HC-J6 (3), and HC-J8 (4), PCR primers were chosen in those regions of little sequence variation.

Primers HCPr52(+): 5'-atgTTGGGTAAGGTCATCGATACCCT-3', HCPr23(+): 5'-CTCATGGGGTAACGTCATCGGTAAGGTCATCGATACCCT-3', and HCPr54(-): 5'-CTATTACCAGTTCATCATCATCATCCCA-3', were synthesized on a 392 DNA/RNA synthesizer (Applied Biosystems). The sets of primers HCPr23/54 and HCPr52/54 were used, but only with the primer set HCPr52/54, PCR fragments could be obtained. This set of primers amplified the sequence from nucleotide 379 to 957 encoding amino acids 127 to 319: 65 amino acids from the carboxyterminus of core and 128 amino acids of E1. The

amplification products GB358-4, GB549-4, and GB809-4 were cloned as described in example 1. The following clones were obtained from the PCR fragments:

From fragment GB358-4: GB358-4-1 (SEQ ID NO 118)

From fragment GB549-4: GB549-4-3 (SEQ ID NO 120)

From fragment GB809-4: GB809-4-3 (SEQ ID NO 122)

An alignment of the type 4 Core/E1 nucleotide sequences with seq ID NO. 118, 120, and 122 with known sequences is presented in Figure 4. The homologies of the type 4 E1 region (without core) with type 1, type 2, type 3, and type 5 prototype sequences are depicted in Table 4. Homologies of 53 to 66% are observed with representative isolates of non-type 4 genotypes. Observed homologies in the E1 region within type 4, between the different subtypes, ranges from 75.2 to 78.4%. The recently disclosed sequences of the core region of Egyptian type 4 isolates (for example EG-29 in Figure 3) described by Simmonds et al. (1993) do not allow alignment with the Gabonese sequences (as described in the present invention) in the NSB region and may belong to different type 4 subtypes(s) as can be deduced from the core sequences. The deduced amino acid sequences with SEQ ID NO 119, 121, and 123 are aligned with other prototype sequences in Figure 5. Again, type-specific variation mainly resides in the variable V regions, designated in the present invention, and therefore, type-4-specific amino acids or V regions will be instrumental in diagnosis and therapeutics for HCV type 4.

# Example 10: The Core/E1 and NS5b regions of new HCV type 2, 3 and 4 subtypes

Samples NE92 (subtype 2d), BE98 (subtype 3c), CAM600 and GB809 (subtype 4e), CAMG22 and CAMG27 (subtype 4f), GB438 (subtype 4h), CAR4/1205 subtype (4i), CAR1/501 (subtype 4j), CAR1/901 (subtype 4?), and GB724 (subtype 4?) were selected from a group of sera that reacted positive but aberrantly in a prototype Line Probe Assay as described earlier (Stuyver et al., 1993). Another type 5a isolate BE100 was also analyzed in the C/E1 region, and yet another type 5a isolate BE96 in the NS5b region. A high-titer of HCV RNA could be detected, enabling cloning of fragments by a single round of PCR. As no sequences from any coding region of these subtypes had been disclosed yet, synthetic oligonucleotides for PCR amplification were chosen in the regions of little sequence variation after aligning the sequences of HCV-1 (Choo et al., 1991), HCV-J(Kato et al., 1990), HC-J6 (Okamoto et al., 1991), HC-J8 (Okamoto et al., 1992), and the other new sequences of the present invention.

The above mentioned sets 1, 2 and 3 (see example 5) of primers were used, but only with set 1, PCR fragments could be obtained from all isolates (except for BE98, GB724, and CAR1/501). This set of primers amplified the sequence from nucleotide 379 to 957 encoding amino acids 127 to 319: 65 amino acids from the carboxyterminus of core and 128 amino acids of E1. With set 3, the core/E1 region from isolate NE92 and BE98 could be amplified, and with set 2, the core region of GB358, GB724, GB809, and CAM600 could be amplified. The amplification products were cloned as described in example 1. The following clones were obtained from the PCR fragments:

From isolate GB724, the clone with SEQ ID NO 193 from the core region.

From isolate NE92, the clone with SEQ ID NO 143

From isolate BE98, the clone from the core/E1 region of which part of the sequence has been analyzed and is given in SEQ ID NO 147,

From isolate CAM600, the clone with SEQ ID NO 167 from the E1 region, or SEQ ID NO 165 from the Core/E1 region as shown in Figure 3,

From isolate CAMG22, the clone with SEQ ID NO 171 from the E1 region as shown in Figure 4,

from isolate GB358, the clone with SEQ ID NO 191 in the core region,.

from isolate CAMG27, the clone with SEQ ID NO 173 from the core/E1 region,

from isolate GB438, the clone with SEQ ID NO 177 from the core/ E1 region,

from isolate CAR4/1205, the clone with SEQ ID NO 179 from the core/E1 region,

from isolate CAR1/901, the clone with SEQ ID NO 181 from the core/ E1 region,

from isolate GB809, the clone GB809-4 with SEQ ID NO 189 from the core/E1 region,

clone GB809-2 with SEQ ID NO 169 from the core/E1 region and the clone with SEQ ID NO 163 from the core region,

and from isolate BE100, the clone with SEQ ID NO 155 from the Core/E1 region as shown in Figure 4.

An alignment of these Core/E1 sequences with known Core/E1 sequences is presented in Figure 4. The deduced amino acid sequences with SEQ ID NO 144, 148, 164, 168, 170, 172, 174, 178, 180, 182, 190, 192, 194, 156, 166 are aligned with other prototype sequences in Figure 5. Again, type-specific variation mainly resides in the variable V regions, designated in the present invention, and therefore, type 2d, 3c and type 4-specific amino acids or V regions will be instrumental in diagnosis and therapeutics for HCV type (subtype) 2d, 3c or the different type 4 subtypes.

The NS5b region of isolates NE92, BE98, CAM600, CAMG22, GB438, CAR4/1205, CAR1/501, and BE96 was amplified with primers HCPr206 and HCPr207 (Table 7). The corresponding clones were cloned and sequenced as in example 1 and the corresponding sequences (of which BE98 was partly sequenced) received the following identification numbers:

NE92: SEQ ID NO 145

BE98: SEQ ID NO 149

CAM600: SEQ ID NO 201 CAMG22: SEQ ID NO 203 GB438: SEQ ID NO 207

CAR4/1205: SEQ ID NO 209 CAR1/501: SEQ ID NO 211

BE95: SEQ ID NO 159 BE96: SEQ ID NO 161

An alignment of these NS5b sequences with known NS5b sequences is presented in Figure 1. The deduced amino acid sequences with SEQ ID NO 146, 150, 202, 204, 206, 208, 210, 212, 160, 162 are aligned with other prototype sequences in Figure 2. Again, subtype-specific variations can be observed, and therefore, type 2d, 3c and type 4-specific amino acids or V regions will be instrumental in diagnosis and therapeutics for HCV type (subtype) 2d, 3c or the different type 4 subtypes.

# Example 11: Genotype-specific reactivity of anti-E1 antibodies (Serotyping)

E1 proteins were expressed from vaccinia virus constructs containing a core/E1 region extending from nucleotide positions 355 to 978 (Core/E1 clones described in previous examples including the primers HCPr52 and HCPr54), and expressed proteins from L119 (after the initiator methionine) to W326 of the HCV polyprotein. The expressed protein was modified upon expression in the appropriate host cells (e.g. HeLa, RK13, HuTK-, HepG2) by cleavage between amino acids 191 and 192 of the HCV polyprotein and by the addition of high-mannose type carbohydrate motifs. Therefore, a 30 to 32 kDa glycoprotein could be observed on western blot by means of detection with serum from patients with hepatitis C.

As a reference, a genotype 1b clone obtained form the isolate HCV-B was also expressed in an identical way as described above, and was expressed from recombinant vaccinia virus vvHCV-11A.

A panel of 104 genotyped sera was first tested for reactivity with a cell lysate containing type 1b protein expressed from the recombinant vaccinia virus vvHCV-11A, and compared with cell lysate of RK13 cells infected with a wild type vaccinia virus ('E1/WT'). The lysates were coated as a 1/20 dilution on a normal ELISA microtiter plate (Nunc maxisorb) and left to react with a 1/20 diluation of the respective sera. The panel consisted of 14 type 1a, 38 type 1b, 21 type 2, 21 type 3a, and 9 type 4 sera. Human antibodies were subsequently detected by a goat anti-human IgG conjugated with peroxidase and the enzyme activity was detected. The optical density values of the E1 and wild type lysates were divided and a factor 2 was taken as the cut-off. The results are given in the table A. Eleven out of 14 type 1a sera (79%), 25 out of 38 type 1b sera (66%), 6 out of 21 (29%), 5 out of 21 (24%), and none of the 9 type 4 or the type 5 serum reacted (0%). These experiments clearly show the high prevalence of anti-E1 antibodies reactive with the type 1 E1 protein in patients infected with type 1 (36/52 (69%)) (either type 1a or type 1b), but the low prevalence or absence in non-type 1 sera (11/52 (21%)).

TABLE A

serum	E1/WT
type 1a	
3748	3.15
3807	3.51
5282	1.99
9321	3.12
9324	2.76
9325	6.12
9326	10.56
9356	1.79
9388	3.5
8366	10.72
8380	2.27
10925	4.02
10936	5.04
10938	1.36

type 1b       5205     2.25       5222     1.33       5246     1.24       5250     13.58       5493     0.87       5573     1.75       8243     1.77       8244     2.05       8316     1.21       8358     5.04       9337     14.47       9410     5       9413     5.51       10905     1.26       10919     5.00       10928     8.72       10929     8.26       10931     2.3       10932     4.41       44     2.37       45     3.14       46     4.37       47     5.68       48     2.97       49     1.18       50     9.85       51     4.51       52     1.11       53     5.20       54     0.98       55     1.48       56     1.06       57     3.85       58     7.6       59     3.28       60     3.23       61     7.82       62     1.92		•
5222       1.33         5246       1.24         5250       13.58         5493       0.87         5573       1.75         8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6              59       3.28	type 1b	
5246       1.24         5250       13.58         5493       0.87         5573       1.75         8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6	11	
5250       13.58         5493       0.87         5573       1.75         8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6	II	
5493       0.87         5573       1.75         8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6          59       3.28         60       3.23         61       7.82	Н	4
5573       1.75         8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	H	
8243       1.77         8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6          59       3.28         60       3.23         61       7.82	41	
8244       2.05         8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	II	
8316       1.21         8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	EI .	
8358       5.04         9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	1	
9337       14.47         9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	II.	
9410       5         9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82		1
9413       5.51         10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	II	
10905       1.26         10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	n ·	
10919       5.00         10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	-	
10928       8.72         10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	11	B .
10929       8.26         10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	11	
10931       2.3         10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	1	
10932       4.41         44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	N	
44       2.37         45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	11	
45       3.14         46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	1	
46       4.37         47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	11	
47       5.68         48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82		
48       2.97         49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	il -	•
49       1.18         50       9.85         51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	II	
50     9.85       51     4.51       52     1.11       53     5.20       54     0.98       55     1.48       56     1.06       57     3.85       58     7.6       59     3.28       60     3.23       61     7.82	II -	<b>?</b>
51       4.51         52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	II -	
52       1.11         53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	H	
53       5.20         54       0.98         55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	B1	1 1
54     0.98       55     1.48       56     1.06       57     3.85       58     7.6       59     3.28       60     3.23       61     7.82	SI.	
55       1.48         56       1.06         57       3.85         58       7.6         59       3.28         60       3.23         61       7.82	lk .	ו אס חו
56     1.06       57     3.85       58     7.6       59     3.28       60     3.23       61     7.82		
58     7.6       59     3.28       60     3.23       61     7.82	56	
59 3.28 60 3.23 61 7.82	57	1
60 3.23 61 7.82		
61 7.82		
1 "		
62   1.92		ľ
	62	1.92

type 2	
23	0.91
24	1.16
25 26	2.51 0.96
27	1.20
28	0.96
29	2.58
30	8.05
31 32	0.92 0.82
33	5.75
34	0.79
35	0.86
36	0.85
37 38	0.76 0.92
-39	1.08
40	2.33
41	2.83
42	1.21
43	0.91
type 3	ŀ
1	6.88
2	1.47
2 3 4 5 6 7 8	3.06
5	6.52 10.24
6	2.72
7	1.11
8	1.54
9.	1.60
10 11	1.21 1.07
12	1.00
13	0.85
14	0.96
15	0.51
16 17	1.00 1.09
18	0.99
19	1.04
20	1.04
21	0.96

type 4	
22	0.87
GB48	0.49
GB113	0.68
GB116	0.73
GB215	0.52
GB358	0.56
GB359	0.71
GB438	1.08
GB516	1.04
type 5	
BE95	0.86

Core/E1 clones of isolates BR36 (type 3a) and BE95 (type 5a) were subsequently recombined into the viruses vvHCV-62 and vvHCV-63, respectively. A genotyped panel of sera was subsequently tested onto cell lysates obtained from RK13 cells infected with the recombinant viruses vvHCV-62 and vvHCV-63. Tests were carried out as described above and the results are given in the table given below (TABLE B). From these results, it can clearly be seen that, although some cross-reactivity occurs (especially between type 1 and 3), the obtained values of a given serum are usually higher on its homologous E1 protein than on an E1 protein of another genotype. For type 5 sera, none of the 5 sera were reactive on type 1 or 3 E1 proteins, while 3 out of 5 were shown to contain anti-E1 antibodies when tested on their homologous type 5 protein. Therefore, in this simple test system, a considerable number of sera can already be serotyped. Combined with the reactivity to type-specific NS4 epitopes or epitopes derived from other type-specific parts of the HCV polyprotein, a serotyping assay may be developed for discriminating the major types of HCV. To overcome the problem of cross-reactivity, the position of cross-reactive epitopes may be determined by someone skilled in the art (e.g. by means of competition of the reactivity with synthetic peptides), and the epitopes evoking cross-reactivity may be left out of the composition to be included in the serotyping assay or may be included in sample diluent to outcompete cross-reactive antibodies.

TABLE B

TABLE B	<del></del>	<del>,</del>	
serum	E11b/WT	E13a/WT	E1 <sup>5a</sup> /WT
type 1b			
8316	0.89	0.59	0.80
8358	2.22	2.65	1.96
9337	1.59	0.96	0.93
9410	16.32	9.60	3.62
9413	9.89	2.91	2.85
10905	1.04	0.96	1.05
10919	3.17	2.56	2.96
10928	4.39	2.28	2.07
10929	2.95	2.07	2.08
10931	3.11	1.49	2.11
5	0.86	0.86	0.96
6 .	3.48	1.32	1.32
<sup>.</sup> 7	6.76	4.00	3.77
8	10.88	3.44	4.04
9	1.76	1.88	1.58
10	9.88	7.48	7.20
11	8.48	8.99	8.45
12	0.76	0.72	0.76
13	5.04	5.67	5.37
14	10.48	10.54	11.22
15	5.18	1.62	1.65
type 3			
8332	3.39	4.22	0.66
10907	3.24	4.39	0.96
10908	0.99	0.94	0.98
10934	0.86	0.90	0.90
10927	2.58	2.71	2.44
8210	0.82	0.80	0.86
8344	1.09	6.66	1.17
8351	1.21	1.29	1.22
30	0.85	4.11	0.98
32	0.85	2.16	1.04
type 5	0.79	0.05	
BE110	0.78 0.79	0.95	1.54
BE95	0. <i>19</i> 0.47	1.01	4.95
BE111	0.47	0.52	0.65
BEIII	1.01	0.75	8.33
BE113	1.01	1.27	2.37
DC113	1.11	1.35	1.60

Table 5. Homologies of new HCV sequences with other known HCV types

Region (nucleotides)	Isolate (type)	la HCV-1	1b HCV-J	2a HC-J6	2b HC-J8	Tl	3a T7	T9	В <b>Б</b> Т10
Core (1-573)	PC (5)	83.8 (91.6)	84.8 (92.1)	82.6 (90.1)	82.4 (89.0)				
E1 (574-957)	HD10 (3) BR36 (3) BR33 (3) PC (5) GB358 (4a) GB549 (4b) GB809 (4c)	61.5 (68.0) 62.0 (66.4) 60.7 (67.2) 61.4 (64.0) 62.5 (69.1) 66.0 (72.2) 63.3 (69.1)		56.5 (53.9) 56.5 (54.7) 54.1 (49.6) 59.4 (54.0) 59.1 (56.4)	53.3 (47.2) 54.4 (54.0)				
NS3 (3856-4209)	PC (5)	74.7 (89)	76.1 (86.4)	76.1 (89.8)	78.0 (89.0)				
NS4 (4892-5292)	BR36 (3) HD 10 (3)	67.8 (78.5) 69.8 (74.6)	69.8 (75.1) 66.6 (69.7)	62.0 (67.5) 57.8 (59.9)	61.7 (66.0) 59.1 (59.9)				
NS4 (4936-5292)	PC (5)	61.3 (62.2)	63.0 (65.5)	52.9 (46.2)	54.3 (43.7)				
NS5b (8023-8235)	BR34 (3) BR36 (3) BR33 (3) GB358 (4a) GB549 (4b) GB809 (4c)	65.7 64.3 65.7 67.7 (76.1) 68.8 (76.1) 68.5 (73.5)		63.9 64.8 64.3 66.5 (70.8) 65.9 (71.7) 67.7 (69.9)	64.3 66.7 64.8 65.6 (71.7) 65.9 (74.4) 67.7 (73.5)	94.8 94.8 94.8	93.9 93.4 93.9	75.6 75.1 76.0	77.0 76.5 77.5

Shown are the nucleotide homologies (the amino-acid homology is given between brackets) for the region indicated in the left column.

Table 6. NS4 sequences of the different genotypes

prototype	ТУРЕ	SYNTHETIC PEPTIDE NS4-1 (NS4a)	SYNTHETIC PEPTIDE NS4-5 (NS4b)	SYNTHETIC PEPTIDE NS4-7 (NS4b)
position->		1 1 6 7 9 0 0 0	1 1 7 7 2 3 0 0	1 1 7 7 3 4 0 0
HCV-1	1a	LSG KPAIIPDREV LY <u>RE</u> FDE	SQHLPYIEQ GMMLAEQFKQ K	LAEQFKQ KALGILQTAS RQA
HCV-J	1b	LSG RPAVIPDREV LYQEFDE	as <u>h</u> ipaieo g <u>wot</u> aeołko k	LAEQFKQ KALGLLQTAT KQA
НС-Ј6	2a	<u>VNO</u> R <u>AV</u> V <u>A</u> PDKEV LY <u>E</u> AFDE	as <u>raal</u> iee go <u>r</u> iae <u>ml</u> ks k	iae <u>mi</u> ks k <u>io</u> gilogas koa
HC-J8	2ь	L <u>ND</u> R <u>VV</u> V <u>A</u> PDKEĽ LY <u>E</u> APDE	as <u>kaal</u> iee g <u>ormaemiks</u> k	MAEMIKS KIQGILQQAT RQA
BR36	3a	L <u>G</u> G KPAI <u>V</u> PDKEV LYQ <u>Q Y</u> DE	sq <u>a</u> apyieq <u>aqv</u> ia <u>h</u> qfke k	tvhółke karcitóűat 666
PC	5	LSG KPAHPDREA LYQQ FDE V	a <u>as</u> lpy <u>md</u> e <u>tra</u> iagqfke k	la <u>g</u> qfke kµlg <u>fis</u> t <u>to</u> <u>qk</u> a

<sup>\*,</sup> residues conserved in every genotype. Underlined amino acids are type-specific, amino acids in italics are unique to type 3 and 5 sequences.

# Table 7

SEQ ID NO	Primer NO (polarity)	Sequence from 5' to 3'
63	HCPr161(+)	5'-ACCGGAGGCCAGGAGAGTGATCTCCTCC-3'
64	HCPr162(-)	5'-GGGCTGCTCTATCCTCATCGACGCCATC-3'
65	HCPr163(+)	5'-GCCAGAGGCTCGGAAGGCGATCAGCGCT-3'
66	HCPr164(-)	5'-GAGCTGCTCTGTCCTCGACGCCGCA-3'
67	HCPr23(+)	5'-CTCATGGGGTACATTCCGCT-3'
68	HCPr54(-)	5'-CTATTACCAGTTCATCATCATATCCCA-3'
69	HCPr116(+)	5'-ttttAAATACATCATGRCITGYATG-3'
<b>7</b> 0	НСРт66(-)	5'-ctattaTTGTATCCCRCTGATGAARTTCCACAT-3'
71	HCPr118(-)	5'actagtcgactaYTGIATICCRCTIATRWARTTCCACAT-3'
72	HCPr117(+)	5'-ttttAAATACATCGCIRCITGCATGCA-3'
73	HCPr119(-)	5'-actagtcgactaRTTIGCIATIAGCCKRTTCATCCAYTG-3'
74	HCPr131(+)	5'-ggaattctagaCCITCITGGGAYGARAYITGGAARTG-3'
75	HCPr130(+)	5'-ggaattctagACIGCITAYCARGCIACIGTITGYGC-3'
76	HCPr134(+)	5'-CATATAGATGCCCACTTCCTATC-3'
77	HCPr3(+)	5'-GTGTGCCAGGACCATC-3'
78	HCPr4(-)	5'-GACATGCATGTCATGATGTA-3'
79	HCPr152(+)	5'-TACGCCTCTTCTATATCGGTTGGGGCCTG-3'
80	HCPr52(+)	5'-atgTTGGGTAAGGTCATCGATACCCT-3'
81	HCPr41(+)	5'-CCCGGGAGGTCTCGTAGACCGTGCA-3'
82	HCPr40(-)	5'-ctattaAAGATAGAGAAAGAGCAACCGGG-3'
124	HCPR206	5'-tggggatcccgtatgatacccgctgctttga-3'
125	HCPR207	5'-ggcggaattcctggtcatagcctccgtgaa-3'
141	HCPR109	5'-tgggatatgatgatgaactggtc-3'
142	HCPR14	5'-ccaggtacaaccgaaccaattgcc-3'

Table 8 : NS4 SEROTYPING

	Type	Type 1 NS4		Type	Type 2 NS4		Type	Type 3 NS4	
serum	1	2	7	1	5	7	1	s	7
type 1a									
101 102 103 104 105 106 107 108	е — — е е е е е е е е е е е е е е е е е	m <del>   </del> m m m m m m m m m	m cu m m m m m m m			m a m m a a a a m m	+ + + + + + + + +	÷ · ÷ ÷ ÷ · - · ·	m m m m m + - 1 m m m

	Type	Type 1 NS4		Typ	Type 2 NS4		Typ	Type 3 NS4	
serum	1	5	7	-	s	7	1	2	7
type 1b									
	<b>;</b>	<b>;</b>	•		1	1	1	!	
112		. 7	٣	•				, ,	۰ ۳
113	7	m		,	•	· -	•		) (°
114	7	٣	<u>س</u>	· ,—	+	. 2	+	_	۳ (
1115	e	<u>س</u>	3		+	· m	. 1	٠,	· (*)
116	8	٣	æ	ı	+	-		•	. –
1117	٣		•	ന	· <b>;</b>	· <b>;</b>	<b>-</b> '+	•	٠,
118	_	7	3	•	<b>+</b>	. ~	· •	<b>*</b> /+	"
119	<b>-</b> '+	7	2	<b>+</b>	<b>+</b>	7	+		
120	,	3	٣	ر. س	+	<b>;</b>		٠,	١ ،
121	<u>س</u>	8	m	<b>+</b>	. 7	. 7	2	7	۳
122	m	3	_	•	_	7	2	-	_
123	m	3	2	•	_	7	,	-	-
124	ю	٣	3		<b>+</b>	7	,	•	7

	7		<b>n</b> •		<u>-</u>	<u>,</u> ,	<b>1</b>	<u> </u>	<u>.</u>		<u> </u>		) (	<u> </u>	. (*)					. ,		, ,	1 7 1 7	<u>.</u>		<del>-</del>
3 NS4	5	-		<b>-</b> 7	<u>'</u>			•			-	, -	• ,		+			. ,	) (							-
Type 3	1	,	<b>y</b> -	<b>→</b> 7	, ,	1	) (		· +		) 1		3 ¥	- +	- -			- ~		٠,		• -	• •	, ,		,
	7	7	· -	• -	• -		•	•	<b>'</b> +		, ,	,	· ;	·	7			. (*	· <b>;</b>		,_			, ,	~	•
Type 2 NS4	80	-	· -	· ;	·		•	•		_	٠,	+	<b>;</b>	; +	. 2		٠,	· (*)		· ‡	. 7	· (**	. –	· ‡	_	
Typ	1	_	-	٠,	,		<b>;</b>	• •	<b>-</b>	• •	,	_	<b>;</b>	· <b>;</b>	7+	·	m	· m	2	,		_		· <del> </del>	۳.	•
	7	3	2	<b>+</b>	· ~	~		_	,	3	7	. 60	3	<b>+</b>	m			•		,	<b>;</b>	+	-/+		ı	
1 NS4	5	3	. 7	7	m	m	2	_	•	3	7	۳	٣	<b>;</b>	m					•	+/-	****	<b>;</b>	,	<del>'</del>	
Type 1	1		_	3	8	7	•	,	ı	3	ı	3	,	<b>;</b>	ю		ю	<b>;</b>	2		•	_	,		,	-
	serum	125	126	127	128	129	130	131	132	133	134	135	136	137	138	type 2a	139	140	141	142	43	44	45	46	47	-

	Type	Type 1 NS4		Type	Type 2 NS4		Type	Type 3 NS4	
serum	1	2	7	1	5	7	1	જ	7
type 2b									
149	•	-/+	<b>-</b> /+	3	m	_	7	<b>;</b>	<b>;</b>
type 3									
150	<b>;</b>	<b>;</b>	<b>;</b>	<b>;</b>	<b>;</b>	<b>+</b>	,	m	n
151	,		·	,		,	7	•	7
152	<b>;</b>	•	1	•	•	,	ю	•	•
153	•	,	•	ı	•	•	ı	-	,
154	<b>-</b>		m	1	-/+	7	2		٣
155	•	7	m	•	7	7	_	_	e.
156	,	•	1		1	٠	•	,	•
157		,	•	<b>-</b>	<b>+</b>	.•	*	7	7
158		•	•	•	_	7	3	7	7
159	,	•	•	i	<b>+</b>	-/+	•	æ	ო
160	ı	•	•	,	<b>;</b>	•	•	2	m
191	•	t	1		-	-	<b>-</b> ;+	٣	7
type 4									
162		•		,	ı		ı	•	•
163	7		,	ı	+	+/-	<b>;</b>	,	•

### REFERENCES

Barany F (1991). Genetic disease detection and DNA amplification using cloned thermostable ligase. Proc Natl Acad Sci USA 88: 189-193.

Bej A, Mahbubani M, Miller R, Di Cesare J, Haff L, Atlas R (1990) Mutiplex PCR amplification and immobilized capture probes for detection of bacterial pathogens and indicators in water. Mol Cell Probes 4:353-365.

Bukh J, Purcell R, Miller R (1992). Sequence analysis of the 5' noncoding region of hepatitis C virus. Proc Natl Acad Sci USA 89:4942-4946.

Bukh J, Purcell R, Miller R (1993). At least 12 genotypes ... PNAS 90,8234-8238.

Cha T, Beal E, Irvine B, Kolberg J, Chien D, Kuo G, Urdea M (1992) At least five related, but distinct, hepatitis C viral genotypes exist. Proc Natl Acad Sci USA 89:7144-7148.

Chan S-W, Simmonds P, McOmish F, Yap P, Mitchell R, Dow B, Follett E (1991) Serological responses to infection with three different types of hepatitis C virus. Lancet 338:1991.

Chan S-W, McOmish F, Holmes E, Dow B, Peutherer J, Follett E, Yap P, Simmonds P (1992) Analysis of a new hepatitis C virus type and its phylogenetic relationship to existing variants. J Gen Virol 73:1131-1141.

Chomczynski P, Sacchi N (1987) Single step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. Anal Biochem 162:156-159.

Choo Q, Richman K, Han J, Berger K, Lee C, Dong C, Gallegos C, Coit D, Medina-Selby A, Barr P, Weiner A, Bradley D, Kuo G, Houghton M (1991) Genetic organization and diversity of the hepatitis C virus. Proc Natl Acad Sci USA 88:2451-2455.

Compton J (1991). Nucleic acid sequence-based amplification. Nature, 350: 91-92.

Duchosal A, Eming S, Fisher P (1992) Immunization of hu-PBL-SCID mice and the resue of human monoclonal Fab fragments through combinatorial libraries. Nature 355:258-262.

Duck P (1990). Probe amplifier system based on chimeric cycling oligonucleotides. Biotechniques 9, 142-147.

Guatelli J, Whitfield K, Kwoh D, Barringer K, Richman D, Gengeras T (1990) Isothermal, in vitro amplification of nucleic acids by a multienzyme reaction modeled after retroviral replication. Proc Natl Acad Sci USA 87: 1874-1878.

Hijikata M, Kato N, Ootsuyama Y, Nakagawa M, Shimotohmo K (1991) Gene mapping of the putative structural region of the hepatitis C virus genome by in vitro processing analysis. Proc Natl Acad Sci USA 88, 5547-5551.

Jacobs K, Rudersdorf R, Neill S, Dougherty J, Brown E, Fritsch E (1988) The thermal stability of oligonucleotide duplexes is sequence independent in tetraalkylammonium salt solutions: application to identifying recombinant DNA clones. Nucl Acids Res 16:4637-4650.

Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, Shimotohno K (1990) Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis. Proc Natl Acad Sci USA 87:9524-9528.

Kwoh D, Davis G, Whitfield K, Chappelle H, Dimichele L, Gingeras T (1989). Transcription-based amplification system and detection of amplified human immunodeficiency virus type 1 with a bead-based sandwich hybridization format. Proc Natl Acad Sci USA, 86: 1173-1177.

Kwok S, Kellogg D, McKinney N, Spasic D, Goda L, Levenson C, Sinisky J, (1990). Effects of primer-template mismatches on the polymerase chain reaction: Human immunodeficiency views type 1 model studies. Nucl. Acids Res., 18: 999.

Landgren U, Kaiser R, Sanders J, Hood L (1988). A ligase-mediated gene detection technique. Science 241:1077-1080.

Lizardi P, Guerra C, Lomeli H, Tussie-Luna I, Kramer F (1988) Exponential amplification of recombinant RNA hybridization probes. Bio/Technology 6:1197-1202.

Lomeli H, Tyagi S, Printchard C, Lisardi P, Kramer F (1989) Quantitative assays based on the use of replicatable hybridization probes. Clin Chem 35: 1826-1831.

Machida A, Ohnuma H, Tsuda F, Munekata E, Tanaka T, Akahane Y, Okamoto H, Mishiro S (1992) Hepatology 16, 886-891.

Maniatis T, Fritsch E, Sambrook J (1982) Molecular cloning: a laboratory manual. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Mori S, Kato N, Yagyu A, Tanaka T, Ikeda Y, Petchclai B, Chiewsilp P, Kurimura T, Shimotohno K (1992) A new type of hepatitis C virus in patients in Thailand. Biochem Biophys Res Comm 183:334-342.

Okamoto H, Okada S, Sugiyama Y, Kurai K, Iizuka H, Machida A, Miyakawa Y, Mayumi M (1991) Nucleotide sequence of the genomic RNA of hepatitis C virus isolated from a human carrier: comparison with reported isolates for conserved and divergent regions. J Gen Virol 72:2697-2704.

Okamoto H, Kurai K, Okada S, Yamamoto K, Lizuka H, Tanaka T, Fukuda S, Tsuda F, Mishiro S (1992) Full-length sequences of a hepatitis C virus genome having poor homology to reported isolates: comparative study of four distinct genotypes. Virology 188:331-341.

Persson M, Caothien R, Burton D (1991). Generation of diverse high-affinity human monoclonal antibodies by repertoire cloning. Proc Natl Acad Sci USA 89:2432-2436.

Saiki R, Gelfand D, Stoffel S, Scharf S, Higuchi R, Horn G, Mullis K, Erlich H (1988). Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science 239:487-491.

Saiki R, Walsh P, Levenson C, Erlich H (1989) Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes (1989) Proc Natl Acad Sci USA

86:6230-6234.

Sano T, Smith C, Cantor C (1992) Immuno-PCR: very sensitive antigen detection by means of specific antibody-DNA conjugates. Science 258:120-122.

Simmonds P, McOmsh F, Yap P, Chan S, Lin C, Dusheiko G, Saeed A, Holmes E (1993), Sequence variability in the 5' non-coding region of hepatitis C virus: identification of a new virus type and restrictions on sequence diversity. J Gen Virology, 74:661-668.

Stuyver L, Rossau R, Wyseur A, Duhamel M, Vanderborght B, Van Heuverswyn H, Maertens G (1993) Typing of hepatitis C virus (HCV) isolates and characterization of new (sub)types using a Line Probe Assay. J Gen Virology, 74: 1093-1102.

Walker G, Little M, Nadeau J, Shank D (1992). Isothermal in vitro amplification of DNA by a restriction enzyme/DNA polymerase system. Proc Natl Acad Sci USA 89:392-396.

Wu D, Wallace B (1989). The ligation amplification reaction (LAR) - amplification of specific DNA sequences using sequential rounds of template-dependent ligation. Genomics 4:560-569.

### **CLAIMS**

- 1. A composition comprising or consisting of at least one polynucleic acid containing 8 or more contiguous nucleotides selected from at least one of the following HCV sequences:
- an HCV type 3 genomic sequence, more particularly in any of the following regions:
  - the region spanning positions 417 to 957 of the Core/E1 region of HCV subtype
     3a,
  - the region spanning positions 4664 to 4730 of the NS3 region of HCV type 3,
  - the region spanning positions 4892 to 5292 of the NS3/4 region of HCV type 3,
  - the region spanning positions 8023 to 8235 of the NS5 region of HCV subtype 3a,
  - an HCV subtype 3c genomic sequence,
- an HCV subtype 2d genomic sequence,
- an HCV type 4 genomic sequence,
- the coding region of HCV subtype 5a,

with said nucleotide numbering being with respect to the numbering of HCV nucleic acids as shown in Table 1, and with said polynucleic acids containing at least one nucleotide difference with known HCV polynucleic acid sequences in the above-indicated regions, or the complement thereof.

- 2. A composition according to claim 1, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV genomic sequences:
- an HCV genomic sequence as having a homology of at least 67%, preferably more than 69%, most preferably 71% or more to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region spanning positions 417 to 957 of the Core/E1 region;
- an HCV genomic sequence as having a homology of at least 65%, preferably more than 67%, most preferably 69% or more to any of the sequences as represented in SEQ ID NO 19, 21, 23, 25 or 27 in the region spanning positions 574 to 957 of the E1 region;
- an HCV genomic sequence, having a homology of at least 79%, more preferably at least 81%, most preferably more than 83% or more to any of the sequences as represented in

- SEQ ID NO 147 in the region spanning positions 1 to 378 of the Core region;
- an HCV genomic sequence having a homology of at least 74%, more preferably at least 76%, most preferably more than 78% or more to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region spanning positions 417 to 957 in the Core/E1 region;
- an HCV genomic sequence having a homology of at least 74%, preferably more than 76%, most preferably 78% or more to any of the sequences as represented in SEQ ID NO 13, 15, 17, 19, 21, 23, 25 or 27 in the region spanning positions 574 to 957 in the E1 region;
- an HCV genomic sequence having a homology of more than 73.5%, preferably more than 74%, most preferably 75% homology to any of the sequence as represented in SEQ ID NO 29 in the region spanning positions 4664 to 4730 of the NS3 region;
- an HCV genomic sequence having a homology of more than 70%, preferably more than 72%, most preferably more than 74% homology to any of the sequences as represented in SEQ ID NO 29, 31, 33, 35, 37 or 39 in the region spanning positions 4892 to 5292 in the NS3/NS4 region;
- an HCV genomic sequence having a homology of more than 95%, preferably 95,5%, most preferably 96% homology to any of the sequences as represented in SEQ ID NO 5, 7, 1, 3, 9 or 11 in the region spanning positions 8023 to 8235 of the NS5 region;
- an HCV genomic sequence of the BR36 subgroup of HCV type 3a having a homology of more than 96%, preferably 96.5%, most preferably 97% homology to any of the sequences as represented in SEQ ID NO 5, 7, 1, 3, 9 or 11 in the region spanning positions 8023 to 8192 of the NS5B region;
- an HCV genomic sequence having a homology of more than 79%, more preferably more than 81%, and most preferably more than 83% to the sequence as represented in SEQ ID NO 149 in the region spanning positions 7932 to 8271 in the NS5B region.
- 3. A composition according to claim 1, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV genomic sequences:
- an HCV genomic sequence having a homology of more than 85%, preferably more than 86%, most preferably more than 87% homology to any of the sequences as represented in SEQ ID NO 41, 43, 45, 47, 49, 51, 53 or 151 in the region spanning positions 1 to 573 of the Core region;

- an HCV genomic sequence having a homology of more than 61%, preferably more than 63%, most preferably more than 65% homology to any of the sequences as represented in SEQ ID NO 41, 43, 45, 47, 49, 51, 53, 153 or 155 in the region spanning positions 574 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 76.5%, preferably of more than 77%, most preferably of more than 78% homology with any of the sequences as represented in SEQ ID NO 55, 57, 197 or 199 in the region spanning positions 3856 to 4209 of the NS3 region;
- an HCV genomic sequence having a homology of more than 68%, preferably of more than 70%, most preferably of more than 72% homology with the sequence as represented in SEQ ID NO 157 in the region spanning positions 980 to 1179 of the E1/E2 region;
- an HCV genomic sequence having a homology of more than 57%, preferably more than 59%, most preferably more than 61% homology to any of the sequences as represented in SEQ ID NO 59 or 61 in the region spanning positions 4936 to 5296 of the NS4 region;
- an HCV genomic sequence having a homology of more than 93%, preferably more than 93.5%, most preferably more than 94% homology to any of the sequences as represented in SEQ ID NO 159 or 161 in the region spanning positions 7932 to 8271 of the NS5B region.
- 4. A composition according to claim 1, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV genomic sequences:
- an HCV genomic sequence having a homology of more than 66%, preferably more than 68%, most preferably more than 70% homology in the E1 region spanning positions 574 to 957 to any of the sequences as represented in SEQ ID NO 118, 120 or 122 in the region spanning positions 1 to 957 of the Core/E1 region;
- an HCV genomic sequence having a homology of more than 71%, preferably more than 72%, most preferably more than 74% homology to any of the sequences as represented in SEQ ID NO 118, 120 or 122 in the region spanning positions 379 to 957;
- an HCV genomic sequence having a homology of more than 85%, preferably more than 86%, most preferably more than 86.5% homology to any of the sequences as represented in SEQ ID NO 183, 185 or 187 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 81%, preferably more than

- 83%, most preferably more than 85% homology to the sequence as represented in SEQ ID NO 189 in the region spanning positions 379 to 957 of the E1 region:
- an HCV genomic sequence having a homology of more than 85%, preferably more than 87%, most preferably more than 89% homology to any of the sequences as represented in SEQ ID NO 167 or 169 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 79%, preferably more than 81%, most preferably more than 83% homology to any of the sequences as represented in SEQ ID NO 171 or 173 in the region spanning positions 379 to 957 of the E1 region:
- an HCV genomic sequence having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ ID NO 175 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 83%, preferably more than 85%, most preferably more than 87% homology to the sequence as represented in SEQ ID NO 177 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 76%, preferably more than 78%, most preferably more than 80% homology to the sequence as represented in SEQ ID NO 179 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ
   ID NO 181 in the region spanning positions 379 to 957 of the E1 region;
- an HCV genomic sequence having a homology of more than 73%, preferably more than 75%, most preferably more than 77% homology to any of the sequences as represented in SEQ ID NO 106, 108, 110, 112, 114, or 116 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 88%, preferably more than 89%, most preferably more than 90% homology to any of the sequences as represented in SEQ ID NO 106, 108, 110, or 112 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 88%, preferably more than 89%, most preferably more than 90% homology to any of the sequences as represented in SEQ ID NO 116 or 201 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 87%, preferably more than

- 89%, most preferably more than 90% homology to the sequence as represented in SEQ ID NO 203 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 85%, preferably more than 87%, most preferably more than 89% homology to the sequence as represented in SEQ ID NO 114 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 86%, preferably more than 87%, most preferably more than 88% homology to the sequence as represented in SEQ ID NO 207 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 84%, preferably more than 86%, most preferably more than 88% homology to the sequence as represented in SEQ
   ID NO 209 in the region spanning positions 7932 to 8271 of the NS5 region;
- an HCV genomic sequence having a homology of more than 81%, preferably more than 83%, most preferably more than 85% homology to the sequence as represented in SEQ ID NO 211 in the region spanning positions 7932 to 8271 of the NS5 region.
- 5. A composition according to claim 1, wherein said polynucleic acids correspond to a nucleotide sequence selected from any of the following HCV genomic sequences:
- an HCV genomic sequence having a homology of more than 78%, preferably more than 80%, most preferably more than 82% homology to the sequence as represented in SEQ ID NO 143 in the region spanning positions 379 to 957 of the Core/E1 region;
- an HCV genomic sequence having a homology of more than 74%, preferably more than 76%, most preferably more than 78% homology to the sequence as represented in SEQ ID NO 143 in the region spanning positions 574 to 957;
- an HCV genomic sequence having a homology of more than 87%, preferably more than 89%, most preferably more than 91% homology to the sequence as represented in SEQ ID NO 145 in the region spanning positions 7932 to 8271 of the NS5B region.
- 6. A composition according to any of claims 1 to 5, wherein said polynucleic acid is liable to act as a primer for amplifying the nucleic acid of a certain isolate belonging to the genotype from which the primer is derived.
- 7. A composition according to any of claims 1 to 5, wherein said polynucleic acid is able to act as a hybridization probe for specific detection and/or classification into types of a

nucleic acid containing said nucleotide sequence, with said oligonucleotide being possibly labelled or attached to a solid substrate.

- 8. Use of a composition according to any of claims 1 to 7 for *in vitro* detecting the presence of one or more HCV genotypes, more particularly for detecting the presence of a nucleic acid of any of the HCV genotypes having a nucleotide sequence as defined in any of claims 1 to 5, present in a biological sample liable to contain them, comprising at least the following steps:
  - (i) possibly extracting sample nucleic acid,
  - (ii) possibly amplifying the nucleic acid with at least one of the primers according to claim 6 or any other HCV type 2, HCV type 3, HCV type 4, HCV type 5 or universal HCV primer,
  - (iii) hybridizing the nucleic acids of the biological sample, possibly under denatured conditions, and with said nucleic acids being possibly labelled during or after amplification, at appropriate conditions with one or more probes according to claim 7, with said probes being preferably attached to a solid substrate,
  - (iv) washing at appropriate conditions,
  - (v) detecting the hybrids formed.
  - (vi) inferring the presence of one or more HCV genotypes present from the observed hybridization pattern.
- 9. A composition consisting of or comprising at least one peptide or polypeptide containing in its sequence a contiguous sequence of at least 5 amino acids of an HCV polyprotein encoded by any of the polynucleic acids according to any of claims 1 to 5.
- 10. A composition according to claim 9, wherein said contiguous sequence contains in its sequence at least one of the following amino acid residues:
- L7, Q43, M44, S60, R67, Q70, T71, A79, A87, N106, K115, A127, A190, S130, V134, G142, I144, E152, A157, V158, P165, S177 or Y177, I178, V180 or E180 or F182, R184, I186, H187, T189, A190, S191 or G191, Q192 or L192 or I192 or V192 or E192, N193 or H193 or P193, W194 or Y194, H195, A197 or I197 or V197 or T197, V202, I203 or L203, Q208, A210, V212, F214, T216, R217 or D217 or E217 or V217, H218 or N218, H219 or V219 or L219, L227 or I227, M231 or E231 or Q231, T232 or D232 or A232 or K232, Q235

or I235, A237 or T237, I242, I246, S247, S248, V249, S250 or Y250, I251 or V251 or M251 or F251, D252, T254 or V254, L255 or V255, E256 or A256, M258 or F258 or V258, A260 or Q260 or S260, A261, T264 or Y264, M265, I266 or A266, A267, G268 or T268, F271 or M271 or V271, I277, M280 or H280, I284 or A284 or L84, V274, V291, N292 or S292, R293 or I293 or Y293, Q294 or R294, L297 or I297 or Q297, A299 or K299 or Q299, N303 or T303, T308 or L308, T310 or F310 or A310 or D310 or V310, L313, G317 or Q317, L333, S351, A358, A359, A363, S364, A366, T369, L373, F376, Q386, I387, S392, I399, F402, I403, R405, D454, A461, A463, T464, K484, Q500, E501, S521, K522, H524, N528, S531, S532, V534, F536, F537, M539, I546, C1282, A1283, H1310, V1312, Q1321, P1368, V1372, V1373, K1405, Q1406, S1409, A1424, A1429, C1435, S1436, S1456, H1496, A1504, D1510, D1529, I1543, N1567, D1556, N1567, M1572, Q1579, L1581, S1583, F1585, V1595, E1606 or T1606, M1611, V1612 or L1612, P1630, C1636, P1651, T1656 or I1656, L1663, V1667, V1677, A1681, H1685, E1687, G1689, V1695, A1700, Q1704, Y1705, A1713, A1714 or S1714, M1718, D1719, A1721 or T1721, R1722, A1723 or V1723, H1726 or G1726, E1730, V1732, F1735, I1736, S1737, R1738, T1739, G1740, Q1741, K1742, Q1743, A1744, T1745, L1746, E1747 or K1747, I1749, A1750, T1751 or A1751, V1753, N1755, K1756, A1757, P1758, A1759, H1762, T1763, Y1764, P2645, A2647, K2650, K2653 or L2653, S2664, N2673, F2680, K2681, L2686, H2692, Q2695 or L2695 or I2695, V2712, F2715, V2719 or Q2719, T2722, T2724, S2725, R2726, G2729, Y2735, H2739, I2748, G2746 or 12746, 12748, P2752 or K2752, P2754 or T2754, T2757 or P2757,

with said notation being composed of a letter representing the amino acid residue by its oneletter code, and a number representing the amino acid numbering according to Kato et al., 1990 as shown in Table 1.

- 11. A composition according to any of claims 9 or 10, wherein said contiguous sequence is selected from any of the following HCV amino acid sequences:
- a sequence having a homology of more than 72%, preferably more than 74%, and most preferably more than 77% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 in the region spanning positions 140 to 319 in the Core/E1 region;
- a sequence having a homology of more than 70%, preferably more than 72%, and most preferably more than 75% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 in the E1 region spanning positions 192 to

319;

- a sequence having a homology of more than 86%, preferably more than 88%, and most preferably more than 90% homology to the amino acid sequences as represented in SEQ ID NO 148 in the region spanning positions 1 to 110 in the Core region;
- a sequence having a homology of more than 76%, preferably more than 78%, most preferably more than 80% to any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40 in the region spanning positions 1646 to 1764 in the NS3/NS4 region;
- a sequence having a homology of more than 81.5%, preferably more than 83%, and most preferably more than 86% homology to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28 in the E1 region spanning positions 192 to 319;
- a sequence having a homology of more than 86%, preferably more than 88%, most preferably more than 90% to the amino acid sequence as represented in SEQ ID NO 150 in the region spanning positions 2645 to 2757 in the NS5B region;
- 12. A composition according to any of claims 9 or 10, wherein said contiguous sequence is selected from any of the following HCV amino acid sequences:
- a sequence having a homology of more than 80%, preferably more than 82%, most preferably more than 84% homology to any of the amino acid sequences as represented in SEQ ID NO 118, 120, and 122 in the region spanning positions 127 to 319,
- a sequence having a homology of more than 73%, preferably more than 75%, most preferably more than 78% homology in the E1 region spanning positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO 118, 120, and 122, in the region spanning positions 127 to 319,
- a sequence having more than 85%, preferably more than 86%, most preferably more than 87% homology to any of the amino acid sequences as represented in SEQ ID NO 118, 120 or 122, in the region spanning positions 192 to 319.
- 13. A composition according to any of claims 9 or 10, wherein said contiguous sequence is selected from any of the following HCV amino acid sequences:
- a sequence having more than 93%, preferably more than 94%, most preferably more than 95% homology in the region spanning Core positions 1 to 191 to any of the amino acid

- sequences as represented in SEQ ID NO 42, 44, 46, 48, 50, 52, 54, or 152;
- a sequence having more than 73%, preferably more than 74%, most preferably more than 76% homology in the region spanning E1 positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO 42, 44, 46, 48, 50, 52, 54, 154 or 156;
- a sequence spanning positions 1286 to 1403 of the NS3 region, with said sequence being characterized as having more than 90%, preferably more than 91%, most preferably more than 92% homology to any of the amino acid sequences represented in SEQ ID NO 56 to 58;
- a sequence spanning positions 1646 to 1764 of the NS3/4 region, with said sequence being characterized as having more than 66%, more particularly 68%, most particularly 70% or more homology to any of the amino acid sequences as represented in SEQ ID NO 60 or 62.
- 14. A composition according to any of claims 9 to 10, wherein said contiguous sequence is selected from any of the following HCV amino acid sequences:
- a sequence having a more than 83%, preferably more than 85%, most preferably more than 87% homology in the region spanning Core positions 1 to 319 to the amino acid sequence as represented in SEQ ID NO 144;
- a sequence having a more than 79%, preferably more than 81%, most preferably more than 84% homology in the region spanning E1 positions 192 to 319 to the amino acid sequence as represented in SEQ ID NO 144;
- a sequence having more than 95%, more particularly 96%, most particularly 97% or more homology to the amino acid sequence as represented in SEQ ID NO 146, in the region spanning positions 2645 to 2757 of the NS5B region.
- 15. A composition according to any of claims 9 to 14, wherein said sequence is selected from the following peptides:

QPTGRSWGQ (SEQ ID NO 93)
RSEGRTSWAQ (SEQ ID NO 220)
RTEGRTSWAQ (SEQ ID NO 221)
SRRQPIPRARRTEGRSWAQ (SEQ ID NO 268)
LEWRNTSGLYVL (SEQ ID NO 83)
VNYRNASGIYHI (SEQ ID NO 126)

QHYRNISGIYHV (SEQ ID NO 127)
EHYRNASGIYHI (SEQ ID NO 128)
IHYRNASGIYHI (SEQ ID NO 224)
VPYRNASGIYHV (SEQ ID NO 84)
VNYRNASGIYHI (SEQ ID NO 225)
VNYRNASGVYHI (SEQ ID NO 226)
VNYHNTSGIYHL (SEQ ID NO 227)
QHYRNASGIYHV (SEQ ID NO 228)
QHYRNVSGIYHV (SEQ ID NO 229)
IHYRNASDGYYI (SEQ ID NO 230)
LQVKNTSSSYMV (SEQ ID NO 231)
VYEADDVILHT (SEQ ID NO 85)
VYETEHHILHL (SEQ ID NO 129)
VYEADHHIMHL (SEQ ID NO 130)
VYETDHHILHL (SEQ ID NO 131)
VYEADNLILHA (SEQ ID NO 86)
VWQLRAIVLHV (SEQ ID NO 232)
VYEADYHILHL (SEQ ID NO 233)
VYETDNHILHL (SEQ ID NO 234)
VYETENHILHL (SEQ ID NO 235)
VFETVHHILHL (SEQ ID NO 236)
VFETEHHILHL (SEQ ID NO 237)
VFETDHHIMHL (SEQ ID NO 238)
VYETENHILHL (SEQ ID NO 239)
VYEADALILHA (SEQ ID NO 240)
VQDGNTSTCWTPV (SEQ ID NO 87)
VQDGNTSACWTPV (SEQ ID NO 241)
VRVGNQSRCWVAL (SEQ ID NO 132)
VRTGNTSRCWVPL (SEQ ID NO 133)
VRAGNVSRCWTPV (SEQ ID NO 134)
EEKGNISRCWIPV (SEQ ID NO 242)
VKTGNQSRCWVAL (SEQ ID NO 243)
VRTGNQSRCWVAL (SEQ ID NO 244)

VKTGNQSRCWIAL (SEQ ID NO 245)

VKTGNVSRCWIPL (SEQ ID NO 247)

VKTGNVSRCWISL (SEQ ID NO 248)

VRKDNVSRCWVQI (SEQ ID NO 249)

VRYVGATTAS (SEQ ID NO 89)

APYIGAPLES (SEQ ID NO 135)

APYVGAPLES (SEQ ID NO 136)

AVSMDAPLES (SEQ ID NO 137)

APSLGAVTAP (SEQ ID NO 90)

APSFGAVTAP (SEQ ID NO 250)

VSQPGALTKG (SEQ ID NO 251)

VKYVGATTAS (SEQ ID NO 252)

APYIGAPVES (SEQ ID NO 253)

AQHLNAPLES (SEQ ID NO 254)

SPYVGAPLEP (SEQ ID NO 255)

SPYAGAPLEP (SEQ ID NO 256)

APYLGAPLEP (SEQ ID NO 257)

APYLGAPLES (SEQ ID NO 258)

APYVGAPLES (SEQ ID NO 259)

VPYLGAPLTS (SEQ ID NO 260)

APHLRAPLSS (SEQ ID NO 261)

APYLGAPLTS (SEQ ID NO 262)

RPRRHQTVQT (SEQ ID NO 91)

QPRRHWTTQD (SEQ ID NO 138)

RPRRHWTTQD (SEQ ID NO 139)

RPRQHATVQN (SEQ ID NO 92)

RPRQHATVQD (SEQ ID NO 263)

SPQHHKFVQD (SEQ ID NO 264)

RPRRLWTTQE (SEQ ID NO 265)

PPRIHETTQD (SEQ ID NO 266)

TISYANGSGPSDDK (SEQ ID NO 267)

16. Recombinant vector, particularly for cloning and/or expression, with said recombinant

vector comprising a vector sequence, an appropriate prokaryotic, eukaryotic or viral promoter sequence followed by the nucleotide sequences as defined in claims 1 to 5, with said recombinant vector allowing the expression of any one of the HCV type 2 and/or HCV type 3 and/or type 4 and/or type 5 derived polypeptides according to any of claims 9 to 15 in a prokaryotic, or eukaryotic host, or in living mammals when injected as naked DNA, and more particularly a recombinant vector allowing the expression of any of the following HCV type 2, HCV type 3, type 4 or type 5 polypeptides spanning the following amino acid positions:

- a polypeptide starting at position 1 and ending at any position in the region between positions 70 and 326, more particularly a polypeptide spanning positions 1 to 70, 1 to 85, positions 1 to 120, positions 1 to 150, positions 1 to 191, positions 1 to 200, for expression of the Core protein, and positions 1 to 263, positions 1 to 326, for expression of the Core and E1 protein;
- a polypeptide starting at any position in the region between positions 117 and 192, and ending at any position in the region between positions 263 and 326, more particularly from positions 119 to 326, for expression of E1, or forms that have the putative membrane anchor deleted (positions 264 to 293 plus or minus 8 amino acids);
- a polypeptide starting at any position in the region between positions 1556 and 1688, and ending at any position in the region between positions 1739 and 1764, for expression of the NS4 regions, more particularly a polypeptide starting at position 1658 and ending at position 1711 for expression of the NS4a antigen, and more particularly, a polypeptide starting at position 1712 and ending between positions 1743 and 1972, for example 1712-1743, 1712-1764, 1712-1782, 1712-1972, 1712 to 1782 and 1902 to 1972 for expression of the NS4b protein or parts thereof.
- 17. A composition according to any of claims 9 to 15, wherein said polypeptide is a recombinant polypeptide expressed by means of an expression vector as defined in claim 16.
- 18. A composition according to any of claims 9 to 15 or 16, for use in a method for immunizing a mammal, preferably humans, against HCV comprising administratering a sufficient amount of the composition possibly accompanied by pharmaceutically acceptable adjuvants, to produce an immune response, more particularly a vaccine composition including HCV type 3 polypeptides derived from the E1, Core, or NS4 region and/or type 4 and/or type 5 and/or type 2 polypeptides.

- 19. Antibody raised upon immunization with a composition according to any of claims 9 to 15, 17 or 18, by means of a process according to claim 18, with said antibody being reactive with any of the polypeptides as defined in any of claims 9 to 15, 17 or 18.
- 20. Process for detecting in vitro HCV present in biological sample liable to contain it, comprising at least the following steps:
  - (i) contacting the biological sample to be analyzed for the presence of HCV antibodies with any of the compositions according to claims 9 to 15, 17 or 18, preferentially in an immobilized form under appropriate conditions which allow the formation of an immune complex, wherein said polypeptide is preferentially in the form of a biotinylated polypeptide and is covalently bound to a solid substrate by means of streptavidin or avidin complexes,
  - (ii) removing unbound components,
  - (iii) incubating the immunecomplexes formed with heterologous antibodies, which specifically bind to the antibodies present in the sample to be analyzed, with said heterologous antibodies having conjugated to a detectable label under appropriate conditions,
  - (iv) detecting the presence of said immunecomplexes visually or by means of densitometry and inferring the HCV serotype(s) present from the observed hybridization pattern.
- 21. Use of a composition according to any of claims 9 to 15, 17 or 18, for incorporation into a serotyping assay for detecting one or more serological types of HCV present in a biological sample liable to contain it, more particularly for detecting E1 and NS4 antigens or antibodies of the different types to be detected combined in one assay format, comprising at least the following steps:
  - (i) contacting the biological sample to be analyzed for the presence of HCV antibodies or antigens of one or more serological types, with at least one of the compositions according to claims 9 to 15, 17 or 18 in an immobilized form under appropriate conditions which allow the formation of an immunecomplex, (wherein said polypeptide is preferentially in the form of a biotinylated polypeptide and is covalently bound to a solid substrate by means of streptavidin or avidin complexes),

- (ii) removing unbound components,
- (iii) incubating the immunecomplexes formed with heterologous antibodies, which specifically bind to the antibodies present in the sample to be analyzed, with said heterologous antibodies having conjugated to a detectable label under appropriate conditions,
- (iv) detecting the presence of said immunecomplexes visually or by means of densitometry and inferring the HCV serological types present from the observed binding pattern.
- 22. A kit for determining the presence of HCV genotypes as defined in any of claims 1 to 5 present in a biological sample liable to contain them, comprising:
  - possibly at least one primer composition containing any primer selected from those defined in claim 6 or any other HCV type 2 and/or HCV type 3 and/or HCV type 4 and/or HCV type 5, or universal HCV primers,
  - at least one probe composition according to claim 7, preferably in combination with other polypeptides or peptides from HCV type 1, type 2 or other types of HCV, with said probes being preferentially immobilized on a solid substrate, and more preferentially on one and the same membrane strip,
  - a buffer or components necessary for producing the buffer enabling hybridization reaction between these probes and the possibly amplified products to be carried out,
  - a means for detecting the hybrids resulting from the preceding hybriziation,
  - possibly also including an automated scanning and interpretation device for infering the HCV genotype(s) present in the sample from the observed hybridization pattern.
- 23. A kit for determining the presence of HCV antibodies according to any of claims 9 to 15, 17 or 18 present in a biological sample liable to contain them, comprising:
  - at least one polypeptide composition according to any of claims 9 to 15, 17 or 18, with said polypeptides being preferentially immobilized on a solid substrate, and more preferentially on one and the same membrane strip,
  - a buffer or components necessary for producing the buffer enabling binding reaction between these polypeptides and the antibodies against HCV present in the biological sample,
  - a means for detecting the immune complexes formed in the preceding binding

94

reaction,

- possibly also including an automated scanning and interpretation device for infering the HCV genotype present in the sample from the observed binding pattern.

SUBSTITUTE SHEET (RULE 26)

95

### SEQUENCE LISTING

- (1) GENERAL INFORMATION:
  - (i) APPLICANT:
    - (A) NAME: Innogenetics sa.
    - (B) STREET: Industriepark Zwijnaarde 7, box 4
    - (C) CITY: Ghent
    - (E) COUNTRY: Belgium
    - (F) POSTAL CODE (ZIP): B-9052
    - (G) TELEPHONE: 00 32 9 241 07 11
    - (H) TELEFAX: 00 32 9 241 07 99
  - (ii) TITLE OF INVENTION: New sequences of hepatitis C virus genotypes for diagnosis, prophylaxis and therapy.
  - (iii) NUMBER OF SEQUENCES: 270
  - (iv) COMPUTER READABLE FORM:
    - (A) MEDIUM TYPE: Floppy disk
    - (B) COMPUTER: IBM PC compatible
    - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
    - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)
- (2) INFORMATION FOR SEQ ID NO: 1:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 213 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    - (B) CLONE: BR34-4-20
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..213
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:
- CTC ACG GAA CGG CTT TAC TGC GGG GGC CCT ATG TTC AAC AGC AAG GGG
  Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly
- GCC CAG TGT GGT TAT CGC CGC TGC CGT GCC AGT GGA GTT CTG CCT ACC
  Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr

wo 9	4/256	01						-							PCT	/EP94/01323
			20					25	96				30			;
AGC Ser	TTC Phe	GGC Gly 35	AAC Asn	ACA Thr	ATC Ile	ACT Thr	TGC Cys 40	TAC Tyr	ATC Ile	AAG Lys	GCC Ala	ACA Thr 45	GCG Ala	GCT Ala	GCA Ala	144
AGG Arg	GCC Ala 50	GCA Ala	GGC Gly	CTC Leu	CGG Arg	AAC Asn 55	CCG Pro	GAC Asp	TTT Phe	CTT Leu	GTC Val 60	TGC Cys	GGA Gly	GAT Asp	GAT Asp	192
					GAG Glu 70											213

- (2) INFORMATION FOR SEQ ID NO: 2:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 71 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly
1 5 10 15

Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr 20 25 30

Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala 35 40 45

Arg Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60

Leu Val Val Val Ala Glu Ser 65 . 70

- (2) INFORMATION FOR SEQ ID NO: 3:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 213 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (vii) IMMEDIATE SOURCE:
    (B) CLONE: BR36-23-18
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..213

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:	3 :	:
------	----------	--------------	-----	----	-----	-----	---

CTC Leu 1	ACG Thr	GĀA Glu	CGG Arg	CTT Leu 5	TAC Tyr	TGC Cys	GGG Gly	GGC Gly	CCT Pro 10	ATG Met	TTC Phe	AAC Asn	AGC Ser	AAG Lys 15	GGG Gly	48
GCC Ala	CAG Gln	TGT Cys	GGT Gly 20	TAT Tyr	CGC Arg	CGC Arg	TGC Cys	CGT Arg 25	GCC Ala	AGT Ser	GGA Gly	GTT Val	CTG Leu 30	CCT Pro	ACC Thr	96
AGC Ser	TTC Phe	GGC Gly 35	AAC Asn	ACA Thr	ATC Ile	ACT Thr	TGC Cys 40	TAC Tyr	ATC Ile	AAG Lys	GCC Ala	ACA Thr 45	GCG Ala	GCT Ala	GCA Ala	144
AGG Arg	GCC Ala 50	GCA Ala	GGC	CTC Leu	CGG Arg	AAC Asn 55	CCG Pro	GAC Asp	TTT Phe	CTT Leu	GTC Val 60	TGC Cys	GGA Gly	GAT Asp	GAT Asp	192
			GTG Val												•	213

## (2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 71 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly

1 5 10 15

Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr

Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala 35

Arg Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60

Leu Val Val Val Ala Glu Ser 65 70

- (2) INFORMATION FOR SEQ ID NO: 5:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 213 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

## WO 94/25601

## PCT/EP94/01323

98	
(ii) MOLECULE TYPE: cDNA	
(iii) HYPOTHETICAL: NO	
(iii) ANTI-SENSE: NO	
(vii) IMMEDIATE SOURCE: (B) CLONE: BR36-23-18	
(ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1213	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:	
CTC ACG GAG CGG CTT TAC TGC GGG GGC CCT ATG TTT AAC AGC AAG GGG Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly 1 5 10	48
GCC CAG TGT GGT TAT CGC CGT TGC CGT GCC AGT GGA GTT CTG CCT ACC Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr 20 25 30	96
AGC TTC GGC AAC ACA ATC ACT TGT TAC ATC AAA GCC ACA GCG GCC GCA Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala 35 40 45	144
AAA GCC GCA GGC CTC CGG AGC CCG GAC TTT CTT GTC TGC GGA GAT GAT Lys Ala Ala Gly Leu Arg Ser Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60 CTG GTC GTG GTG GCT GAG AGT	192
Leu Val Val Ala Glu Ser 65 70	213
(2) INFORMATION FOR SEQ ID NO: 6:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 71 amino acids</li> <li>(B) TYPE: amino acid</li> <li>(D) TOPOLOGY: linear</li> </ul>	
(ii) MOLECULE TYPE: protein	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:	
Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly  1 5 10 15	
Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr	

Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala

40

35

30

45

WO 94/25601 . PCT/EP94/01323

Lys Ala Ala Gly Leu Arg Ser Pro Asp Phe Leu Val Cys Gly Asp Asp
50 55 60

Leu Val Val Val Ala Glu Ser 65 70

- (2) INFORMATION FOR SEQ ID NO: 7:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 213 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: CDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:

(B) CLONE: BR36-23-20

- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..213
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

CTC ACG GAG CGG CTT TAC TGC GGG GGC CCT ATG TTT AAC AGC AAA GGG
Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly

1 5 10 15

GCC CAG TGT GGT TAT CGC CGT TGC CGT GCC AGT GGA GTT CTG CCT ACC
Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr
20 25 30

AGC TTC GGC AAC ACA ATC ACT TGT TAC ATC AAA GCC ACA GCG GCC GCA
Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala
35
40
45

AAA GCC GCA GGC CTC CGG AGC CCG GAC TTT CTT GTC TGC GGA GAT GAT
Lys Ala Ala Gly Leu Arg Ser Pro Asp Phe Leu Val Cys Gly Asp Asp
50 55 60

CTG GTC GTG GCT GAG AGT
Leu Val Val Val Ala Glu Ser
65 70

- (2) INFORMATION FOR SEQ ID NO: 8:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 71 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear

192

									100							
	(1	i) M	OLEC	ULE '	TYPE	: pro	tei	n							•	
	(x	i) S	BQUE	NCE I	DESCI	RIPTI	ON:	SEQ	ID 1	10: 1	B :					• .
	u Th: 1	r Glı	u Ar		u Tyz 5	c Cys	Gl <sub>y</sub>	y Gly	Pro		t Phe	e Ası	Ser	Lys 15	Gly	
Ala	a Gli	n Cys	Gl <sub>3</sub>		r Arg	J Arg	Cys	Arg 25		Ser	c Gly	v Val	. Leu 30		Thr	•
Se	r Phe	e Gly 35		1 Thi	r Ile	Thr	Cys 40		Ile	Lys	3 Ala	Thr 45		Ala	Ala	
Lys	Ala 50	a Ala	Gly	/ Let	ı Arg	Ser 55		) Asp	Phe	Lev	Val		Gly	, yab	Asp	
Let 65		Val	. Val	. Ala	70	Ser										•
(2)	INE	ORMA	TION	FOF	SEQ	ID	NO:	9:								
٠	(ii	(	B) I C) S D) I	YPE : TRAN OPOL	nuc IDEDN OGY :	leic ESS: line	aci sin ear	.đ	s							
	(iii	) HY	איייסס	アヤエへ	AL:	NIO.										
					: NO											
٠	(vii				SOUR	CE: 33-2-	-17									
	(ix		A) N	AME/	KEY: ION:	CDS 12	213				-		·			
	(xi	) SE(	QUEN	CB D	ESCR:	IPTIC	ON:	SEQ 1	ID NO	): 9	:					
CTC Leu 1	ACG Thr	GAG Glu	CGG Arg	CTT Leu 5	TAC Tyr	TGC Cys	GGG Gly	GGC Gly	CCT Pro 10	ATG Met	TTC Phe	AAC Asn	AGC Ser	AAG Lys 15	GGG Gly	48
GCC Ala	CAG Gln	TGT Cys	GGT Gly 20	TAT Tyr	CGC Arg	CGT Arg	TGT Cys	CGT Arg 25	GCC Ala	AGT Ser	GGA Gly	GTT Val	CTG Leu 30	CCT Pro	ACC Thr	96
AGT Ser	TTC Phe	GGC Gly	AAC Asn	ACA Thr	ATC Ile	ACT Thr	TGT Cys	TAC Tyr	ATC Ile	AAG Lys	GCC Ala	ACA Thr	GCG Ala	GCT Ala	GCA Ala	144

40

AAA GCC GCA GGC CTC CGG AAC CCG GAC TTT CTT GTT-TGC GGA GAT GAT

35

WO 94/25601 PCT/EP94/01323

101

Lys Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60

TTG GTC GTG GTG GCT GAG AGT Leu Val Val Val Ala Glu Ser 65 70

213

- (2) INFORMATION FOR SEQ ID NO: 10:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 71 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly
1 5 10 15

Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr
20 25 30

Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala 35 40 45

Lys Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60

Leu Val Val Val Ala Glu Ser

- (2) INFORMATION FOR SEQ ID NO: 11:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 213 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: CDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:

(B) CLONE: BR33-2-21

- (ix) FEATURE:
  - \_\_ (A) NAME/KEY: CDS
    - (B) LOCATION: 1..213
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

102

CTC	ACG	GAG	CGG	CTT	TAC	TGC	GGG	GGC	CCT	ATG	TTC	AAC	AGC	AAG	GGG	4.8
Leu	Thr	Glu	Arg	Leu	Tyr	Сув	Gly	Gly	Pro	Met	Phe	Asn	Ser	Lys	Gly	
1				5					10					15	-	
GCC	CAG	TGT	GGT	TAT	CGC	CGT	TGT	CGT	GCC	AGT	GGA	GTT	CTG	CCT	ACC	96
Ala	Gln	Cys	Gly	Tyr	Arg	Arg	Cys	Arg	Ala	Ser	Gly	Val	Leu	Pro	Thr	
			20					25			_		30			
AGT	TTC	GGC	AAC	ACA	ATC	ACT	TGT	TAC	ATC	AAG	GCC	ACA	GCG	GCT	GCA	144
Ser	Phe	Gly	Asn	Thr	Ile	Thr	Cys	Tyr	Ile	Lys	Ala	Thr	Ala	Ala	Ala	
		35					40			_		45				
AAA	GCC	GCA	GGC	CTC	CGG	AAC	CCG	GAC	TTT	CTT	GTT	TGC	GGA	GAT	GAT	192
Lys	Ala	Ala	Gly	Leu	Arg	Asn	Pro	Asp	Phe	Leu	Val	Суз	Glv	Asp	Asp	
	50	•				55					60	•	•			
TTG	GTC	GTG	GTG	GCT	GAG	AGT										213
Leu	Val	Val	Val	Ala	Glu	Ser										-13
65					70											

- (2) INFORMATION FOR SEQ ID NO: 12:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 71 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Leu Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly
1 5 10 15

Ala Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr 20 25 30

Ser Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Ala Ala Ala 35 40 45

Lys Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp 50 55 60

Leu Val Val Val Ala Glu Ser 65 70

- (2) INFORMATION FOR SEQ ID NO: 13:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 541 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO

WO 94/25601 PCT/EP94/01323

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:
(B) CLONE: HD10-2-5

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 2..541

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

CG	TC ( /al (	GC (	SCT C	ro V	TA G al G 5	GA G	GC G	TC G	la A	GA G rg A	CC C	TT G eu A	CG C	is G	GC ly 15	46
GTG Val	AGG Arg	GCC Ala	CTT Leu	GAA Glu 20	_Asp	GGG Gly	ATA Ile	AAT Asn	Phe 25	Ala	ACA Thr	GGG Gly	AAT Asn	TTG Leu 30	CCC	94
GGT Gly	TGC Cys	TCC Ser	Phe	TCT	ATC Ile	TTC Phe	CTT	CTT Leu 40	GCT Ala	CTG Leu	TTC Phe	TCT	TGC Cys 45	TTA Leu	ATC	142
CAT His	Pro	GCA Ala 50	GCT	AGT Ser	CTA Leu	GAG Glu	TGG Trp 55	CGG Arg	AAC Asn	ACG Thr	TCT Ser	GGC Gly 60	CTC	TAT Tyr	GTC Val	190
CTT	ACC Thr 65	Asn	GAC Asp	TGT Cys	TCC Ser	AAT Asn 70	AGC Ser	AGT Ser	ATT Ile	GTG Val	TAT Tyr 75	GAG Glu	GCC Ala	GAT Asp	GAC Asp	238
GTT Val 80	Ile	CTG	CAC	ACA Thr	CCC Pro 85	GGC Gly	TGT Cys	GTA Val	CCT Pro	TGT Cys 90	GTT Val	CAG Gln	GAC Asp	GGT Gly	AAT Asn 95	286
ACA Thr	TCT Ser	GCG Ala	TGC Cys	TGG Trp 100	ACC Thr	CCA Pro	GTG Val	ACA Thr	CCT Pro 105	ACA Thr	GTG Val	GCA Ala	GTC Val	AGG Arg 110	TAC Tyr	334
GTC Val	GGA Gly	GCA Ala	ACC Thr 115	ACC Thr	GCT Ala	TCG Ser	ATA Ile	CGC Arg 120	AGG Arg	CAT His	GTA Val	GAC Asp	ATG Met 125	TTG Leu	GTG Val	382
GGC Gly	GCG Ala	GCC Ala 130	ACG Thr	ATG Met	TGC Cys	TCT Ser	GCT Ala 135	CTC Leu	TAC Tyr	GTG Val	GGT Gly	GAT Asp 140	ATG Met	TGT Cys	GGG Gly	. 430
GCC Ala	GTC Val 145	TTC Phe	CTC Leu	GTG Val	GGA Gly	CAA Gln 150	GCC Ala	TTC Phe	ACG Thr	TTC Phe	AGA Arg 155	CCT Pro	CGT Arg	CGC Arg	CAT His	478
CAA Gln 160	ACG Thr	GTC Val	CAG Gln	ACC Thr	TGT Cys 165	AAC Asn	TGC Cys	TCA Ser	CTG Leu	TAC Tyr 170	CCA Pro	GGC Gly	CAT His	CTT Leu	TCA Ser 175	526

GGA CAC CGA ATG GCT Gly His Arg Met Ala 180

541

### (2) INFORMATION FOR SEQ ID NO: 14:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 180 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val 1 5 10 15

Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro Gly 20 25 30

Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Phe Ser Cys Leu Ile His
35 40 45

Pro Ala Ala Ser Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val Leu 50 55 60

Thr Asn Asp Cys Ser Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Val 65 70 75 80

Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Gln Asp Gly Asn Thr 85 90 95

Ser Ala Cys Trp Thr Pro Val Thr Pro Thr Val Ala Val Arg Tyr Val 100 105 110

Gly Ala Thr Thr Ala Ser Ile Arg Arg His Val Asp Met Leu Val Gly
115 120 125

Ala Ala Thr Met Cys Ser Ala Leu Tyr Val Gly Asp Met Cys Gly Ala 130 135 140

Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg Arg His Gln 145 150 155 160

Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser Gly 165 170 175

His Arg Met Ala 180

## (2) INFORMATION FOR SEQ ID NO: 15:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 541 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

WO 94/25601 PCT/EP94/01323

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:

(B) CLONE: HD10-2-14

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 2..541

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

C (	TC ( /al (	GC 6	CT (	Pro V	TA G al G 5	GA G	GC G	TC G	CA A	GA G LTG A 10	CC C	TT G	CG C	is G	GC ly 15	46
GTO	AGG	GCC	CTI	' GAA	GAC	GGG	ATA	AAT	TTC	GCA	ACA	GGG	AAT	TTG	ccc	94
Val	. Arg	, Ala	Leu	. Glu 20	Asp	Gly	Ile	Asn	Phe 25	Ala	Thr	Gly	' Asn	Leu 30	Pro	,
GGT	TGC	TCC	TTT	TCT	ATC	TTC	CTT	CCT	GCT	CIG	TTC	TCI	TGC	TTA	ATC	142
Gly	Cys ·	Ser	Phe 35		Ile	Phe	Leu	Pro 40		Leu	Phe	Ser	Cys 45	Leu	Ile	
CAT	CCA	GCA	GCT	AGT	CTA	GAG	TGG	CGG	AAC	ACG	TCT	GGC	CTC	TAT	GTC	190
His	Pro	Ala 50	Ala	Ser	Leu	Glu	Trp 55	Arg	Asn	Thr	Ser	Gly 60	Leu	Tyr	Val	
CTT	ACC	AAC	GAC	TGT	TCC	AAT	AGC	AGT	ATT	GTG	TAT	GAG	GCC	GAT	GAC	238
Leu	Thr 65	Asn	Asp	Cys	Ser	Asn 70	Ser	Ser	Ile	Val	Tyr 75		Ala	Asp	Asp	
GTT	ATT	CTG	CAC	ACA	CCC	GGC	TGT	GTA	CCT	TGT	GTT	CAG	GAC	GGT	AAT	286
Val 80	Ile	Leu	His	Thr	Pro 85	Gly	Cys	Val	Pro	Cys 90	Val	Gln	Asp	Gly	Asn 95	
ACA	TCT	GCG	TGC	TGG	ACC	CCA	GTG	ACA	CCT	ACA	GTG	GCA	GTC	AGG	TAC	334
Thr	Ser	Ala	Сув	Trp 100	Thr	Pro	Val	Thr	Pro 105	Thr	Val	Ala	Val	Arg 110	Tyr	
GTC	GGA	GCA	ACC	ACC	GCT	TCG	АТА	CGC	AGG	СУТ	СТА	GAC	እጥአ	באתונים	Cutto	382
Val	Gly	Ala	Thr 115	Thr	Ala	Ser	Ile	Arg 120	Arg	His	Val	Asp	Ile 125	Leu	Val	362
GGC	GCG	GCC	ACA	ATG	TGC	TCT	GCT	CTC	TAC	GTG	GGT	GAT	ATG	тст	GGG	430
Gly	Ala	Ala 130	Thr	Met	Cys	Ser	Ala 135	Leu	Tyr	Val	Gly	Asp 140	Met	Сув	Gly	430
GCC	GTC	TTC	CTC	GTG	GGA	CAA	GCC	TTC	ACG	TTC	AGA	ССТ	CGT	CGC	САТ	478
Ala	Val 145	Phe	Leu	Val	Gly	Gln 150	Ala	Phe	Thr	Phe	Arg 155	Pro	Arg	Arg	His	370
CAA	ACG	GTC	CAG	ACC	TGT	AAC	TGC	TCA	CTG	TAC	CCA	GGC	CAT	CTT	TCA	526

WO 94/25601 PCT/EP94/01323

106

Gln Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser 160 165 170 175

GGA CAC CGA ATG GCT Gly His Arg Met Ala 180

541

- (2) INFORMATION FOR SEQ ID NO: 16:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 180 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val 1 5 10 15

Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro Gly
20 25 30

Cys Ser Phe Ser Ile Phe Leu Pro Ala Leu Phe Ser Cys Leu Ile His

Pro Ala Ala Ser Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val Leu 50 55 60

Thr Asn Asp Cys Ser Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Val 65 70 75 80

Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Gln Asp Gly Asn Thr
85 90 95

Ser Ala Cys Trp Thr Pro Val Thr Pro Thr Val Ala Val Arg Tyr Val 100 105 110

Gly Ala Thr Thr Ala Ser Ile Arg Arg His Val Asp Ile Leu Val Gly
115 120 125

Ala Ala Thr Met Cys Ser Ala Leu Tyr Val Gly Asp Met Cys Gly Ala 130 135 140

Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg His Gln 145 150 155 160

Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser Gly 165 170 175

His Arg Met Ala 180

- (2) INFORMATION FOR SEQ ID NO: 17:
  - (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 541 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:

(B) CLONE: HD10-2-21

(ix) FEATURE:

(A) NAME/KEY: CDS (B) LOCATION: 2..541

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

C G	TC G al G	GC G	CT C	CT G	TA G al G 5	GA G	GC G	TC G	CA A	GA G rg A	ICC C	TT G	ICG C	is G	GC ly 15	46
GTG Val	AGG Arg	GCC Ala	CT1	GAA Glu 20	Asp	GGG	ATA	AAT Asn	TTC Phe 25	Ala	ACA Thr	Gly	AAT Asn	TTG Leu 30	CCC Pro	94
GGT Gly	TGC Cys	TCC Ser	Phe	Ser	ATC Ile	TTC Phe	CTT Leu	CTT Leu 40	Ala	CTG	TTC Phe	TCT	TGC Cys 45	TTA Leu	ATC Ile	142
CAT His	CCA Pro	GCA Ala 50	GCT Ala	AGT Ser	CTA Leu	GAG Glu	TGG Trp 55	CGG Arg	AAC Asn	ACG Thr	TCT Ser	GGC Gly 60	CTC Leu	TAC Tyr	GTC Val	190
CTT Leu	ACC Thr 65	AAC Asn	GAC Asp	TGT Cys	TCC Ser	AAT Asn 70	AGC Ser	AGT Ser	ATT Ile	GTG Val	TAT Tyr 75	GAG Glu	GCC Ala	GAT Asp	GAC Asp	238
GTT Val 80	ATT Ile	CTG Leu	CAC His	ACA Thr	CCC Pro 85	GGC Gly	TGT Cys	GTA Val	CCT Pro	TGT Cys 90	GTT Val	CAG Gln	GAC Asp	GGT Gly	AAT Asn 95	286
ACA Thr	TCT Ser	GCG Ala	TGC Cys	TGG Trp 100	ACC Thr	CCA Pro	GTG Val	ACA Thr	CCT Pro 105	ACA Thr	GTG Val	GCA Ala	GTC Val	AGG Arg 110	TAC Tyr	334
GTC Val	GGA Gly	GCA Ala	ACC Thr 115	ACC Thr	GCT Ala	TCG Ser	ATA Ile	CGC Arg 120	AGG Arg	CAT His	GTA Val	GAC Asp	ATA Ile 125	TTG Leu	GTG Val	382
GGC Gly	GCG Ala	GCC Ala 130	ACG Thr	ATG Met	TGC Cys	TCT Ser	GCT Ala 135	CTC Leu	TAC Tyr	GTG Val	GGT Gly	GAT Asp 140	ATG Met	TGT Cys	GGG Gly	430

WO 94/25601 PCT/EP94/01323 108 GCC GTC TTC CTC GTG GGA CAA GCC TTC ACG TTC AGA CCT CGT CGC CAT Ala Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg Arg His 145 150 CAA ACG GTC CAG ACC TGT AAC TGC TCA CTG TAC CCA GGC CAT CTT TCA 526 Gln Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser GGA CAC CGA ATG GCT 541 Gly His Arg Met Ala (2) INFORMATION FOR SEQ ID NO: 18: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 180 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18: Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Phe Ser Cys Leu Ile His 40 Pro Ala Ala Ser Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val Leu Thr Asn Asp Cys Ser Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Val Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Gln Asp Gly Asn Thr Ser Ala Cys Trp Thr Pro Val Thr Pro Thr Val Ala Val Arg Tyr Val 100 Gly Ala Thr Thr Ala Ser Ile Arg Arg His Val Asp Ile Leu Val Gly 120 Ala Ala Thr Met Cys Ser Ala Leu Tyr Val Gly Asp Met Cys Gly Ala 130 Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg Arg His Gln 150 Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser Gly 170 His Arg Met Ala

180

(2) INFORMATION FOR SEC ID NO: 19							
	19	NO ·	TD	SEO	EUB.	TNFORMATION	(2)

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 541 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:
  - (B) CLONE: BR36-9-13
- (ix) FEATURE:

115

- (A) NAME/KEY: CDS
- (B) LOCATION: 2..541

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

C G	TC G al G	GC G ly A	CT C la P	CC G	TA G al G	GA G ly G	GC G ly V	TC G al A	la A	GA G rg A 10	CC C	TT G eu A	CG C. la H	is G	GC ly 15	46
GTG Val	AGG Arg	GCC Ala	CTT	GAA Glu 20	GAC Asp	GGG Gly	ATA Ile	AAT Asn	TTC Phe 25	GCA Ala	ACA Thr	GGG Gly	AAT Asn	TTG Leu 30	Pro	94
GGT Gly	TGC Cys	TCC Ser	TTT Phe 35	TCT	ATT Ile	TTC Phe	CTT	CTT Leu 40	GCT Ala	CTG Leu	TTC Phe	TCT Ser	TGC Cys 45	TTA Leu	ATT Ile	142
CAT His	CCA Pro	GCA Ala 50	GCT Ala	AGT Ser	CTA Leu	GAG Glu	TGG Trp 55	CGG Arg	AAT Asn	ACG Thr	TCT Ser	GGC Gly 60	CTC Leu	TAT Tyr	GTC Val	190
CTT Leu	ACC Thr 65	AAC Asn	GAC Asp	TGT Cys	TCC Ser	AAT Asn 70	AGC Ser	AGT Ser	ATT Ile	GTG Val	TAC Tyr 75	GAG Glu	GCC Ala	GAT Asp	GAC Asp	238
GTT Val 80	ATT Ile	CTG Leu	CAC His	ACA Thr	CCC Pro 85	GGC Gly	TGC Cys	ATA Ile	CCT Pro	TGT Cys 90	GTC Val	CAG Gln	GAC Asp	GGC Gly	AAT Asn 95	286
ACA Thr	TCC Ser	ACG Thr	TGC Cys	TGG Trp 100	ACC Thr	CCA Pro	GTG Val	ACA Thr	CCT Pro 105	ACA Thr	GTG Val	GCA Ala	GTC Val	AAG Lys 110	TAC Tyr	334
GTC Val	GGA Gly	GCA Ala	ACC	ACC Thr	GCT Ala	TCG Şer	ATA Ile	CGC Arg	AGT Ser	CAT His	GTG Val	GAC Asp	CTA Leu	TTA Leu	GTG Val	382

120

wo 9	4/256	01													PCT/	EP94/01323	3
								1	110								
			. Thr					Leu					Met		GGG	43	0
		. Phe					Ala					Pro			CAT	47	8
	Thr					Asn					Pro				TCA Ser 175	52	6
			ATG Met													54	1
(2)	INF	(i) (	TION SEQU A) L B) T	ENCE ENGT YPE :	CHA H: 1 ami	RACT 80 ai	ERIS mino cid	TICS	-								
٠	(ii	) MO	LECU	LE T	YPE:	pro	tein										
Val 1			QUEN Pro									Ala	His	Gly 15	Val		
Arg	Ala	Leu	Glu 20	qaA	Gly	Ile	Asn	Phe 25	Ala	Thr	Gly	Asn	Leu 30	Pro	Gly	·	
Сув	Ser	Phe 35	Ser	Ile	Phe	Leu	Leu 40	Ala	Leu	Phe	Ser	Cys 45	Leu	Ile	His		
Pro	Ala 50	Ala	Ser	Leu	Glu	Trp 55	Arg	Asn	Thr	Ser	Gly 60	Leu	Tyr	Val	Leu		
Thr 65	Asn	Asp	Cys	Ser	Asn 70	Ser	Ser	Ile	Val	Tyr 75	Glu	Ala	Ąsp	Asp	Val 80		
Ile	Leu	His	Thr	Pro 85	Gly	Сув	Ile	Pro	Сув 90	Val	Gln	Asp	Gly	Asn 95	Thr		
Ser	Thr	Сув	Trp 100	Thr	Pro	Val	Thr	Pro 105	Thr	Val	Ala	Val	Lys 110	Tyr	Val		
Gly	Ala	Thr 115	Thr	Ala	Ser	Ile	Arg 120	Ser	His	Val	Asp	Leu 125	Leu	Val	Gly		
Ala	Ala 130	Thr	Met	Сув	Ser	Ala 135	Leu	Tyr -	Val	Gly	Asp 140	Met	Сув	Gly	Ala		
Val 145	Phe	Leu	Val	Gly	Gln 150	Ala	Phe	Thr	Phe	Arg 155	Pro	Arg	Arg	His	Gln 160		
Thr	Val	Gln	Thr	Суз	Asn	Суз	Ser	Leu	Tyr	Pro	Gly	His	Leu	Ser	Glv		

WO 94/25601

PCT/EP94/01323

111

165

170

175

His Arg Met Ala 180

### (2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 541 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO.
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:

(B) CLONE: BR36-9-20

- . (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 2..541

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

C GTC GGC GCT CCC GTA GGA GGC GTC GCA AGA GCC CTT GCG CAT GGC Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly  1 5 10 15	46
GTG AGG GCC CTT GAA GAC GGG ATA AAT TTC GCA ACA GGG AAT TTG CCC Val Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro 20 25 30	94
GGT TGC TCC TTT TCT ATT TTC CTT CTT GCT CTG TTC TCT TGC TTA ATT Gly Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Phe Ser Cys Leu Ile 35 40 45	142
CAT CCA GCA GCT AGT CTA GAG TGG CGG AAT ACG TCT GGC CTC TAT GTC His Pro Ala Ala Ser Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val	190

50 55 60

CTT ACC AAC GAC TGT TCC AAT AGC AGT ATT GTG TAC GAG GCC GAT GAC

CTT ACC AAC GAC TGT TCC AAT AGC AGT ATT GTG TAC GAG GCC GAT GAC
Leu Thr Asn Asp Cys Ser Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp
65 70 75

GTT ATT CTG CAC ACA CCC GGC TGC ATA CCT TGT GTC CAG GAC GGC AAT

Val Ile Leu His Thr Pro Gly Cys Ile Pro Cys Val Gln Asp Gly Asn

80 85 90 95

ACA TCC ACG TGC TGG ACC CCA GTG ACA CCT ACA GTG GCA GTC AAG TAC
Thr Ser Thr Cys Trp Thr Pro Val Thr Pro Thr Val Ala Val Lys Tyr
100 105 110

<b>VO</b> 9	4/256	01				•			112	-	٠.				PCT/EP94	/01323
GT(	GG/	A GC/ / Ala	A ACC Thr 115	Thr	GCT Ala	TCG Ser	ATA Ile	CGC Arg	Ser	CAT His	GTG Val	GAC Asp	CTA Leu 125	Leu	GTG Val	382
GGC	GCG Ala	GCC Ala 130	C ACG	Met	TGC Cys	TCT Ser	GCG Ala 135	Leu	TAC	GTG Val	GCT	GAC Asp 140	Met	TGT Cys	GGG Gly	430
GCT Ala	GTC Val	Phe	CTC Leu	GTG Val	GGA Gly	CAA Gln 150	Ala	TTC Phe	ACG Thr	TTC	AGA Arg 155	Pro	CGT Arg	CGC Arg	CAT His	478
CAA Gln 160	Thr	GTC Val	CAG Gln	ACC	TGT Cys 165	Asn	TGC Cys	TCG Ser	CTG Leu	TAC Tyr 170	CCA Pro	GGC	CAT His	CTT Leu	TCA Ser 175	526
			ATG Met													541
(2)	INF	orma	TION	FOR	SEQ	ID 1	NO:	22:								
٠		()	SEQUI A) Li B) T D) T	ENGT: YPE: OPOL	H: 1: ami: OGY:	80 ar no ac line	mino cid ear									
			LECUI QUENC					SEQ :	ID NO	D: 2:	2:					
Val 1			Pro									Ala	His	Gly 15	Val	
Arg	Ala	Leu	Glu 20	Asp	Gly	Ile	Asn	Phe 25	Ala	Thr	Gly	Asn	Leu 30	Pro	Gly	
Cys	Ser	Phe 35	Ser	Ile	Phe	Leu	Leu 40	Ala	Leu	Phe	Ser	Сув 45	Leu	Ile	His	
Pro	Ala 50	Ala	Ser	Leu	Glu	Trp 55	Arg	Asn	Thr	Ser	Gly 60	Leu	Tyr	Val	Leu	
Thr 65	Asn	Asp	Cys	Ser	Asn 70	Ser	Ser	Ile	Val	Tyr 75	Glu	Ala	Asp	Asp	Val 80	
			Thr	85					90					95		
Ser	Thr	Сув	Trp 100	Thr	Pro	Val	Thr	Pro 105	Thr	Val	Ala	Val	Lys 110	Tyr	Val	
Gly	Ala	Thr 115	Thr	Ala	Ser		Arg 120		His	Val	qaA	Leu 125	Leu	Val	Gly	
Ala	Ala 130	Thr	Met	Сув	Ser	Ala 135	Leu	Tyr	Val	Gly	Asp 140	Met	Сув	Gly	Ala	

WO 94/25601 PCT/EP94/01323 113 Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg Arg His Gln Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser Gly 170 His Arg Met Ala (2) INFORMATION FOR SEQ ID NO: 23: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 541 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (vii) IMMEDIATE SOURCE: (B) CLONE: BR33-1-10 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 2..541 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23: C GTC GGC GCT CCC GTA GGA GGC GTC GCA AGA GCC CTT GCG CAT GGC 46 Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly GTG AGG GCC CTT GAG GAC GGG ATA AAC TTC GCA ACA GGG AAT TTG CCC 94 Val Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro 25 GGT TGC TCC TTT TCT ATC TTC CTT CTT GCT CTG TTC TCT TGC TTA ATC 142 Gly Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Phe Ser Cys Leu Ile 40 CAT CCA GCA GCT GGT CTA GAG TGG CGG AAT ACG TCT GGC CTC TAT GTC 190 His Pro Ala Ala Gly Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val CTT ACC AAC GAC TGT TCC AAT AGT AGT ATT GTG TAT GAG GCC GAT GAC 238 Leu Thr Asn Asp Cys Ser Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp 70 GTT ATT CTG CAC GCG CCC GGC TGT GTA CCT TGT GTC CAG GAC GGC AAT 286 Val Ile Leu His Ala Pro Gly Cys Val Pro Cys Val Gln Asp Gly Asn 85 90

WO 94/25601		•	114			PCT/EP94/01323
ACG TCT ACA T Thr Ser Thr C	rgc TGG ACC Cys Trp Thr 100	CCA GTA	ACA CCT Thr Pro	Thr Val Al	A GTC AGG a Val Arg	Tyr
GTC GGG GCA A Val Gly Ala T 1						
GGC GCG GCC A Gly Ala Ala T 130	ACG ATG TGC Thr Met Cys	TCT GCG Ser Ala 135	Leu Tyr	GTG GGT GA Val Gly As	p Met Cys	GGG 430
GCC GTC TTC C Ala Val Phe L 145	TC GTG GGA eu Val Gly	CAA GCC Gln Ala 150	TTC ACG	TTC AGA CC Phe Arg Pr 155	C CGC CGC o Arg Arg	CAT 478
CAA ACG GTC C Gln Thr Val G 160	AG ACC TGT In Thr Cys 165	AAC TGC Asn Cys	TCG CTG Ser Leu	TAC CCA GG Tyr Pro Gl 170	C CAT CTI y His Leu	TCA 526 Ser 175
GGA CAT CGC A Gly His Arg M	<del>-</del>					541
(A) (B) (D)	QUENCE CHAI LENGTH: 18 TYPE: amin TOPOLOGY: CULE TYPE: ENCE DESCRI	30 amino no acid linear protein	acids	D: 24:		
(X1) SEQUI			-		a His Gly 15	Val
Arg Ala Leu G		Ile Asn		Thr Gly Ası		Gly
Cys Ser Phe Se	er Ile Phe	Leu Leu 40	Ala Leu	Phe Ser Cys	_	His
Pro Ala Ala Gl 50	ly Leu Glu	Trp Arg 55	Asn Thr	Ser Gly Let	ı Tyr Val	Leu
Thr Asn Asp Cy 65	ys Ser Asn 70	Ser Ser	Ile Val	Tyr Glu Ala 75	Asp Asp	Val
.Ile Leu His Al	la Pro Gly 85	Cys Val	Pro Cys 90	Val Gln Ası	Gly Asn 95	Thr
Ser Thr Cys Tr		Val Thr	Pro Thr 105	Val Ala Val	Arg Tyr 110	Val
Gly Ala Thr Th	nr Ala Ser	Ile Arg	Ser His	Val Asp Lev	Leu Val	Gly

	1	15	I CIIDIPAIODA
115	120	125	
Ala Ala Thr Met C	ys Ser Ala Leu Tyr 135	Val Gly Asp Met	Cys Gly Ala
Val Phe Leu Val G 145	ly Gln Ala Phe Thr 150	Phe Arg Pro Arg	Arg His Gln 160
	ys Asn Cys Ser Leu 65	Tyr Pro Gly His	Leu Ser Gly 175
His Arg Met Ala 180			
(2) INFORMATION FO	OR SEQ ID NO: 25:		
(A) LEN( (B) TYPI (C) STRJ	CHARACTERISTICS: STH: 541 base pair E: nucleic acid ANDEDNESS: single DLOGY: linear	s	
(ii) MOLECULE	TYPE: cDNA		
(iii) HYPOTHETI	ICAL: NO		
(iii) ANTI-SENS	SE: NO		
(vii) IMMEDIATE (B) CLON	S SOURCE: IE: BR33-1-19		
	C/KEY: CDS TION: 2541		
(xi) SEQUENCE	DESCRIPTION: SEQ	ID NO: 25:	
C GTC GGC GCT CCC Val Gly Ala Pro	GTA GGA GGC GTC GG Val Gly Gly Val Al 5	CA AGA GCC CTT GCC a Arg Ala Leu Ala 10	G CAT GGC 4 A His Gly 15
GTG AGG GCC CTT GA Val Arg Ala Leu Gl	u Asp Gly Ile Asn	TTC GCA ACA GGG A Phe Ala Thr Gly A 25	AAT TTG CCC 9. Asn Leu Pro 30
GGT TGC TCT TTT TC Gly Cys Ser Phe Ser 35	T ATC TTC CTT CTT r lle Phe Leu Leu 40	GCT CTG TTC TCT T Ala Leu Phe Ser C	GC TTA ATC 14: Cys Leu Ile 45
CAT CCA GCA GCT GG His Pro Ala Ala Gly 50	T CTA GAG TGG CGG y Leu Glu Trp Arg 55	AAT ACG TCT GGC C Asn Thr Ser Gly I 60	TC TAT GTC 190 eu Tyr Val
CTT ACC AAC GAC TGT Leu Thr Asn Asp Cys 65	T TCC AAT AGT AGT S Ser Asn Ser Ser 70	ATT GTG TAT GAG G Ile Val Tyr Glu A 75	CC GAT GAC 238

WO 9	4/256	01				٠		•	116	-					PCT/E	P94/01323
GTT Val 80	. Ile	CTC	G CAC	GCG Ala	Pro 85	Gly	TGT Cys	GTA Val	CCI Pro	TGT Cys 90	Val	CAG Glm	GAC Asp	GGC Gly	AAT Asn 95	286
ACG	TCT Sei	Thi	TGC Cys	TGG Trp 100	Thr	CCA Pro	GTA Val	ACA Thr	CCT Pro 105	Thr	GTG Val	GCA Ala	GTC Val	AGG Arg 110	Tyr	334
GTC Val	GG(	GCA Ala	ACC Thr 115	Thr	GCT Ala	TCG Ser	ATA Ile	CGC Arg 120	Ser	CAT	GTG Val	GAC Asp	CTG Leu 125	TTA Leu	GTA Val	382
GGC	GCG	GCC Ala 130	ACG Thr	ATG Met	TGC Cys	TCT Ser	GCG Ala 135	CTT Leu	TAC	GTG Val	GGT Gly	GAT Asp 140	ATG Met	TGT Cys	GGG	430
GCC Ala	GTC Val 145	Phe	CTC Leu	GTG Val	GGA Gly	CAA Gln 150	GCC Ala	TTC Phe	ACG Thr	TTC Phe	AGA Arg 155	CCC Pro	CGC Arg	CGC Arg	CAT His	478
CAA Gln 160	ACG Thr	GTC Val	CAG Gln	ACC Thr	TGT Cys 165	AAC Asn	TGC Cys	TCG Ser	CTG Leu	TAC Tyr 170	CCA Pro	GGC Gly	CAT His	CTT Leu	TCA Ser 175	<b>526</b>
			ATG Met													541
(2)			TION SEQUI						•							
		()	A) LI B) TY D) TY	ENGTI (PE :	H: 18 amir	30 an	nino cid									
			LECUI													
Val 1			Pro						Arg			Ala	His		Val	
•	Ala	Leu	Glu 20	_	Gly	Ile	Asn	Phe 25	10 Ala	Thr	Gly	Asn	Leu 30	Pro	Gly	
Cys	Ser	Phe 35	Ser	Ile	Phe	Leu	Leu 40	Ala	Leu	Phe	Ser	Cys 45	Leu	Ile	His	
Pro	Ala 50	Ala	Gly	Leu	Glu	Trp 55	Arg	Asn	Thr	Ser	Gly 60	Leu	Tyr	Val	Leu	
Thr 65	Asn	Asp	Cys	Ser	Asn 70	Ser	Ser	Ile	Val	Tyr 75	Glu	Ala	Asp	Asp	Val 80	
Ile	Leu	His	Ala	Pro 85	Gly	Сув	Val	Pro	Сув 90	Val	Gln	Asp	Gly	Asn 95	Thr	

WO 94/25601 PCT/EP94/01323 117 Ser Thr Cys Trp Thr Pro Val Thr Pro Thr Val Ala Val Arg Tyr Val 105 Gly Ala Thr Thr Ala Ser Ile Arg Ser His Val Asp Leu Leu Val Gly 120 Ala Ala Thr Met Cys Ser Ala Leu Tyr Val Gly Asp Met Cys Gly Ala 135 Val Phe Leu Val Gly Gln Ala Phe Thr Phe Arg Pro Arg Arg His Gln 145 155 Thr Val Gln Thr Cys Asn Cys Ser Leu Tyr Pro Gly His Leu Ser Gly 170 His Arg Met Ala (2) INFORMATION FOR SEQ ID NO: 27: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 541 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (vii) IMMEDIATE SOURCE: (B) CLONE: BR33-1-20 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 2..541 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27: C GTC GGC GCT CCC GTA GGA GGC GTC GCA AGA GCC CTT GCG CAT GGC 46 Val Gly Ala Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly GTG AGG GCC CTT GAG GAC GGG ATA AAC TTC GCA ACA GGG AAT TTG CCC 94 Val Arg Ala Leu Glu Asp Gly Ile Asn Phe Ala Thr Gly Asn Leu Pro GGT TGC TCT TTT TCT ATC TTC CTT CTT GCT CTG TTC TCT TGC TTA ATC Gly Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Phe Ser Cys Leu Ile 40 CAT CCA GCA GCT GGT CTA GAG TGG CGG AAT ACG TCT GGC CTC TAT GTC

His Pro Ala Ala Gly Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val 55

WO 9	4/256	01				•		1	18						PCT/I	EP94/01323
CTI	ACC Thi	: Ası	GAC Asp	TGT	TCC	AAT Asn 70	AGT Ser	AGT Ser	ATI	GTG Val	TAT Tyr 75	Glu	GCC	GAT Asp	GAC Asp	238
	Ile		CAC His								Val					286
			TGC Cys							Thr					Tyr	334
GTC Val	GGG	GCA Ala	ACC Thr 115	ACC Thr	GCT Ala	TCG Ser	ATA Ile	CGC Arg 120	Ser	CAT	GTG Val	GAC Asp	CTG Leu 125	TTA Leu	GTA Val	382
GGC	GCG	GCC Ala 130	ACG Thr	ATG Met	TGC Cys	TCT Ser	GCG Ala 135	CTT	TAC Tyr	GTG Val	GGT Gly	GAT Asp 140	ATG Met	TGT Cys	GGG	430
GCC Ala	GTC Val 145	TTC Phe	CTC Leu	GTG Val	GGA Gly	CAA Gln 150	GCC Ala	TTC Phe	ACG Thr	TTC Phe	AGA Arg 155	CCC Pro	CGC Arg	CGC Arg	CAT His	478
CAA Gln 160	ACG Thr	GTC Val	CAG Gln	ACC Thr	TGT Cys 165	AAC Asn	TGC Cys	TCG Ser	CTG Leu	TAC Tyr 170	CCA Pro	GGC Gly	CAT His	CTT Leu	TCA Ser 175	526
			ATG Met	_												541
(2)		(i) (i) () (i)	FION SEQUE L) LE S) TY O) TO	NCE NGTE PE:	CHAR I: 18 amir	ACTE O am	RIST ino id	rics								
			UENC					EQ 1	ID NO	): 28	ı:					
Val			Pro									Ala	His	Gly 15	Val	
Arg	Ala	Leu	Glu . 20	Asp	Gly	Ile .	Asn	Phe 25	Ala	Thr	Gly	Asn	Leu 30		Gly	
Сув	Ser	Phe 35	Ser	Ile	Phe	Leu	Leu 40	Ala	Leu	Phe	Ser	Cys 45	Leu	Ile	His	
Pro	Ala 50	Ala	Gly :	Leu	Glu	Trp : 55	Arg	Asn	Thr	Ser	Gly 60	Leu	Tyr	Val	Leu	
Thr 65	Asn	Asp	Cys :	Ser .	Asn 70	Ser :	Ser	Ile	Val	Tyr 75	Glu	Ala	Asp	Asp	Val 80	

O 94.	/2560	1				•		1	19						PCT/EP94/01
Ile	Leú	His	Ala	Pro 85	Gly	Cys	Val	Pro	Сув 90	Val	Gln	Asp	Gly	Asn 95	Thr
Ser	Thr	Cys	Trp 100	Thr	Pro	Val	Thr	Pro 105	Thr	Val	Ala	Val	Arg 110	Tyr	Val .
Gly	Ala	Thr 115	Thr	Ala	Ser	Ile	Arg 120	Ser	His	Val	Asp	Leu 125	Leu	Val	Gly
Ala	Ala 130	Thr	Met	Сув	Ser	Ala 135	Leu	Tyr	Val	Gly	Asp 140	Met	Сув	Gly	Ala
Val 145	Phe	Leu	Val	Gly	Gln 150	Ala	Phe	Thr	Phe	Arg 155	Pro	Arg	Arg	His	Gln 160
Thr '	Val	Gln	Thr	Сув 165	Asn	Cys	Ser	Leu	Tyr 170	Pro	Gly	His	Leu	Ser 175	Gly
His .	Arg	Met	Ala 180												
(2)	INFO	RMAT	'ION	FOR	SEQ	ID N	IO: 2	29:							
		SEQ (A (B	UENC L) LE L) TY E) ST	E CH NGTH PE: RAND	ARAC : 28 nucl	TERI 7 ba eic SS:	STIC se p acid sing	CS: pairs	ı						
•	(i)	SEQ (A (B (C	UENC LE TY	E CH NGTH PE: RAND POLO	ARAC : 28 nucl EDNE GY:	TERI 7 ba eic SS: line	STIC se p acid sing ar	CS: pairs	ı						
•	(i) (ii)	SEQ (A (B (C (D	(UENC L) LE L) TY L) ST L) TO	E CH NGTH PE: RAND POLO	ARAC : 28 nucl EDNE GY:	TERI 7 ba eic SS: line	STIC se p acid sing ar	CS: pairs							
(1)	(i) (ii) lii)	SEQ (A (B (C (D MOL	(UENC ) LE () TY () ST () TO	E CH NGTH PE: RAND POLO E TY	EARAC : 28 nucl EDNE GY: PE:	TERI 7 ba eic SS: line	STIC se p acid sing ar	CS: pairs	ı						
t) t)	(i) (ii) Lii)	SEQ (A (B (C (D MOL HYP ANT	OTHE	E CHENGTHE PE: RANDPOLO E TY TICA NSE:	EARACE: 28 nucl EDNE GY: PE: L: N NO	TERI 7 ba eic SS: line cDNA	STIC se p acid sing ar	CS: pairs							
t) t) v)	(i) (ii) lii) iii)	SEQ (A (B (C (D MOL HYP ANT IMM (B	QUENCAL DESCRIPTION OF THE COLL OTHE I-SE	TE CHENGTHE PE: RANDOPOLO E TY TICA NSE: TE SO ONE:	EY: (	TERI 7 ba eic SS: line cDNA O	ser pacid	CS: pairs							

191

Asp Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala

CAC TTT CTG TCA CAG ACT AAG CAG CAG GGA CTC AAC TTC TCG TTC CTG His Phe Leu Ser Gln Thr Lys Gln Gln Gly Leu Asn Phe Ser Phe Leu

ACT GCC TAC CAA GCC ACT GTG TGC GCT CGC GCG CAG GCT CCT CCC CCA
Thr Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro
35 40 45
AGT TGG GAC GAG ATG TGG AAG TGT CTC GTA CGG CTT AAG CCA ACA CTA

120

Ser Trp Asp Glu Met Trp Lys Cys Leu Val Arg Leu Lys Pro Thr Leu 50 55 60

CAT GGA CCT ACG CCT CTT CTA TAT CGG TTG GGG CCT GTC CAA AAT GAA 239
His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Pro Val Gln Asn Glu
65 70 75

ATC TGC TTG ACA CAC CCC ATC ACA AAA TAC ATC ATG GCA TGC ATG TCA

11e Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser

80 85 90 95

- (2) INFORMATION FOR SEQ ID NO: 30:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 95 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Asp Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His

1 10 15

Phe Leu Ser Gln Thr Lys Gln Gln Gly Leu Asn Phe Ser Phe Leu Thr
20 25 30

Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Ser 35 40 45

Trp Asp Glu Met Trp Lys Cys Leu Val Arg Leu Lys Pro Thr Leu His
50 55 60

Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Pro Val Gln Asn Glu Ile
65 70 75 80

Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser 85 90 95

- (2) INFORMATION FOR SEQ ID NO: 31:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 401 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    - (B) CLONE: HD10-1-25

ť	ix	FEATURE:	
١		, realure:	

(A) NAME/KEY: CDS

(B) LOCATION: 3..401

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

TC	CAA Gln	AAT Asn	GAA Glu	ATC Ile	TGC	TTG	ACA	CAC	CCC	GTC	ACA	AAA	TAC	ATT	ATG	47
	1				5			1120	FIO	10	1111	гуя	ıyr	TTG	net 15	
GCA	TGC	ATC	TCA	GCT	GAT	CIG	GAA	GTA	ACC	ACC	: AGC	: ACC	TGG	GTG	TTG	95
Ala	Сув	Met	: Ser	Ala 20	Asp	Leu	Glu	val	Thr 25		Ser	Thr	Trp	Val 30	Leu	
CTT	GGA	GGG	GTC	CTC	GCG	GCC	CTA	GCG	GCC	TAC	TGC	TTG	TCA	GTC	GGC	143
Leu	Gly	Gly	Val 35	Leu	Ala	Ala	Leu	Ala 40	Ala	Tyr	Сув	Leu	Ser 45	Val	Gly	
TGC	GTT	GTA	ATC	GTG	GGT	CAT	ATC	GAG	CTG	GGG	GGC	AAG	CCG	GCA	CTC	191
Cys	Val	Val 50	Ile	Val	Gly	His	Ile 55	Glu	Leu	Gly	Gly	Fys	Pro	Ala	Leu	
GTT	CCA	GAC	AAG	GAG	GTG	TTG	TAT	CAA	CAG	TAC	GAT	GAG	ATG	GAG	GAG	239
Val	Pro 65	Asp	Lys	Glu	Val	Leu 70	Tyr	Gln	Gln	Tyr	Asp 75	Glu	Met	Glu	Glu	
TGC	TCG	CAA	GCC	GCC	CCA	TAC	ATC	GAA	CAA	GCT	CAG	GTA	ATA	GCC	CAC	287
Cys 80	Ser	Gln	Ala	Ala	Pro	Tyr	Ile	Glu	Gln	Ala	Gln	Val	Ile	Ala	His	
80					85					90					95	
CAG	TTC	AAG	GAG	AAA	ATC	CTT	GGA	CTG	CTG	CAG	CGA	GCC	ACC	ממי	CAA	335
Gln	Phe	Lys	Glu	Lys	Ile	Leu	Gly	Leu	Leu	Gln	Arg	Ala	Thr	Gln	Gln	335
				100					105					110		
CAA	GCT	GTC	ATT	GAG	CCC	GTA	ATA	GCT	TCC	AAC	TCC	CDD	nnc.	متعلم	CRR	202
Gln	Ala	Val	Ile	Glu	Pro	Val	Ile	Ala	Ser	Asn	Trp	Gln	Lvs	Leu	Glu	383
		.*	115					120					125			
				AAG												401
Thr	Phe		His	Lys	His				•							-77
		130														

## (2) INFORMATION FOR SEQ ID NO: 32:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 133 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Gln Asn Glu Ile Cys Leu Thr His Pro Val Thr Lys Tyr Ile Met Ala 1 5 10 15

		122			ICI/LI74/UDE
Cys Met Ser Ala		Val Thr Thr 25	Ser Thr Trp	Val Leu 30	Leu
Gly Gly Val Leu 35	Ala Ala Leu	Ala Ala Tyr 40	Cys Leu Ser	Val Gly	Cys
Val Val Ile Val 50	. Gly His Ile 6	Glu Leu Gly	Gly Lys Pro 60	Ala Leu	Val
Pro Asp Lys Glu 65	Val Leu Tyr ( 70	Gln Gln Tyr	Asp Glu Met 75	Glu Glu	Cys 80
Ser Gln Ala Ala	Pro Tyr Ile (	Glu Gln Ala 90	Gln Val Ile	Ala His 95	Gln
Phe Lys Glu Lys 100		Leu Leu Gln 105	Arg Ala Thr	Gln Gln 110	Gln
Ala Val Ile Glu 115 Phe Trp His Lys 130	:	Ala Ser Asn 120	Trp Gln Lys 125	Leu Glu	Thr
(2) INFORMATION	FOR SEQ ID NO	0: 33:			
(A) L (B) T (C) S	CE CHARACTERIS ENGTH: 401 bas YPE: nucleic a TRANDEDNESS: a OPOLOGY: line	se pairs acid single	·		
(ii) MOLECU	LE TYPE: cDNA				
(iii) HYPOTH	ETICAL: NO		•		
(iii) ANTI-S	ense: No				
(vii) IMMEDIA (B) CI	ATE SOURCE: LONE: HD10-1-3	3		-	
	E: AME/KEY: CDS OCATION: 340	)1			
(xi) SEQUENO	CE DESCRIPTION	: SEQ ID NO	: 33:		
TC CAA AAT GAA A Gln Asn Glu 1 1	ATC TGC TTG AC Lle Cys Leu Th 5	r His Pro V	TC ACA AAA T al Thr Lys T 10	yr Ile M	TG 47 et 15

GCA TGC ATG TCA GCT GAT CTG GAA-GTA ACC ACC AGC ACC TGG GTG TTG

Ala Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu

20

95

143

WO 94	/2560	1				•		1	23						PCT/I	EP94/01323
Leu	Gly	Gly	Val		u Ala	a Ala	a Lei	u Ala	a Al	а Ту	r Cy	s Le			l Gly	
TGC	GTT	GTA	ATC	GI	G GG	CA!	T ATC	4 C GA	G CTY	G GG	G GG	C AA	4! G CC	- - GC	A CTC	. 191
		50					5	5			•	6	D		a Leu	
GTT Val	Pro 65	Asp Asp	AAG Lys	GA(	GT(	Let 70	туз	r CAJ	A CAG	TAC Ty:	C GAS	p Glu	3 ATO	G GAC	G GAG	239
TGC Cys 80	TCG Ser	CAA Gln	GCC Ala	GC0 Ala	CCZ Pro 85	Туг	Ile	GAZ Glu	A CAI	A GC: 1 Ala 90	a Gl	G GT/	A ATZ	A GCC	CAC His 95	287
CAG Gln	TTC Phe	AAG Lys	GAG Glu	AAA Lys 100	Ile	CTI Leu	GGA Gly	CTC Lev	CTC Lev 105	Glr	G CG/	A GCC J Ala	ACC Thr	CAA	CAA Gln	335
CAA Gln	GCT Ala	GTC Val	ATT Ile 115	GAG Glu	CCC Pro	GTA Val	ATA Ile	GCT Ala 120	Ser	AAC Asr	TG(	G CAA	AAG Lys 125	Leu	GAA Glu	383
ACC Thr								-								401
(2)		i) S (A (B	EQUE	NCE NGT	SEQ CHA H: 1 ami:	RACT: 33 ai	ERIS mino cid	TICS								
	(īi)			•	YPE:											
	(xi)	SEQ	UENC	E D	ESCR:	IPTIC	ON: S	SEQ. :	ID N	0: 3	4:					
Gln 1	Asn (	Glu	Ile	Cys 5	Leu	Thr	His	Pro	Val 10	Thr	Lys	Tyr	Ile	Met 15	Ala	
Cys N	let :	Ser .	Ala 20	Asp	Leu	Glu	Val	Thr 25	Thr	Ser	Thr	Trp	Val 30	Leu	Leu	
Gly G	Sly '	Val :	Leu .	Ala	Ala	Leu	Ala 40	Ala	Tyr	Сув	Leu	Ser 45	Val	Gly	Сув	•
Val V	7al 1	[le	Val	Gly	His	Ile 55	Glu	Leu	Gly	Gly	Lys 60	Pro	Ala	Leu	Val	
Pro A 65	rab I	jys (	3lu '	Val	Leu 70	Tyr	Gln	Gln	Tyr	Asp 75	Glu	Met	Glu	Glu	Cys 80	•
Ser G	ln A	la 1	la :	Pro 85	Tyr	Ile	Glu	Gln	Ala 90	Gln	Val	Ile	Ala	His 95	Gln	
Phe L	ys G	lu I	ys :	Ile	Leu	Gly	Leu	Leu	Gln	Arg	Ala	Thr	Gln	Gln	Gln	

100 105 110

Ala Val Ile Glu Pro Val Ile Ala Ser Asn Trp Gln Lys Leu Glu Thr 115 120 125

Phe Trp His Lys His 130

- (2) INFORMATION FOR SEQ ID NO: 35:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 401 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:

(B) CLONE: BR36-20-164

- (ix) FEATURE:
  - (A) NAME/KBY: CDS
  - (B) LOCATION: 3..401
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

TC CAA															47
Gln	Asn	Glu	Ile	Cys	Leu	Thr	His	Pro	Ile	Thr	Lys	Tyr	Ile	Met	
1				5					10					15	

- GCA TGC ATG TCA GCT GAT CTG GAA GTA ACC ACC AGC ACC TGG GTT TTG

  Ala Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu

  20 25 30
- CTT GGA GGG GTC CTC GCG GCC CTA GCG GCC TAC TGC TTG TCA GTC GGT
  Leu Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly
  35 40 45
- TGT GTT GTG ATT GTG GGT CAT ATC GAG CTG GGG GGC AAG CCG GCA ATC

  Cys Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile

  50 60
- GTT CCA GAC AAA GAG GTG TTG TAT CAA CAA TAC GAT GAG ATG GAA GAG
  Val Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu
  65 70 75
- TGC TCA\_CAA GCT GCC CCA TAT ATC GAA CAA GCT CAG GTA ATA GCT CAC

  Cys Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His

  80 90 95

CAG TTC AAG GGA AAA GTC CTT GGA TTG CTG CAG CGA GCC ACC CAA CAA 335

125

Gln Phe Lys Gly Lys Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln 100 105 110

CAA GCT GTC ATT GAG CCC ATA GTA ACT ACC AAC TGG CAA AAG CTT GAG
Gln Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu
115 120 125

GCC TTT TGG CAC AAG CAT Ala Phe Trp His Lys His 130

401

- (2) INFORMATION FOR SEQ ID NO: 36:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 133 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Gln Asn Glu Ile Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala 1 5 10 15

Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu Leu 20 25 30

Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly Cys 35 40 45

Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile Val
50 55 60

Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu Cys 65 70 75 80

Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln 85 90 95

Phe Lys Gly Lys Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln Gln 100 105 110

Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu Ala 115 120 125

Phe Trp His Lys His 130

- (2) INFORMATION FOR SEQ ID NO: 37:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 401 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

### (vii) IMMEDIATE SOURCE:

(B) CLONE: BR36-20-166

#### (ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 3..401

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

TC	CAA Gln 1	AAT Asn	GAA Glu	ATC Ile	TGC Cys 5	TTG Leu	ACA Thr	CAC His	CCC Pro	ATC Ile 10	ACA Thr	AAA Lys	TAC Tyr	ATC Ile	ATG Met 15	47
GCA Ala	TGC Cys	ATG Met	TCA Ser	GCT Ala 20	Asp	CTG Leu	GAA Glu	A GTA L Val	ACC Thr 25	Thr	AGC Ser	ACC Thr	TGG	GTI Val	TTG Leu	<b>95</b>
CTT	GGA Gly	GGG Gly	GTC Val 35	Leu	GCG Ala	GCC Ala	CTA Leu	GCG Ala 40	Ala	TAC	TGC Cys	TTG Leu	TCA Ser 45	Val	GGT	143
TGT Cys	GTT Val	GTG Val 50	Ile	GTG Val	GGT Gly	CAT His	Ile 55	Glu	CTG Leu	GGG Glÿ	GGC	Lys 60	Pro	GCA Ala	ATC	191
GTT Val	CCA Pro 65	GAC Asp	AAA Lys	GAG Glu	GTG Val	TTG Leu 70	Tyr	CAA Gln	CAA Gln	TAC	GAT Asp 75	Glu	ATG Met	GAA Glu	GAG Glu	239
TGC Cys 80	TCA Ser	CAA Gln	GCT Ala	GCC Ala	CCA Pro . 85	TAT	ATC Ile	GAA Glu	CAA Gln	GCT Ala 90	Gln	GTG Val	ATA Ile	GCT Ala	CAC His 95	287
CAG Gln	TTC Phe	AAG Lys	GAA Glu	AAA Lys 100	GTC Val	CTT Leu	GGA Gly	TTG Leu	CTG Leu 105	CAG Gln	CGA Arg	GCC Ala	ACC Thr	CAA Gln 110	CAA Gln	335
CAA Gln	GCT Ala	GTC Val	ATT Ile 115	GAG Glu	CCC Pro	ATA Ile	GTA Val	ACT Thr 120	ACC Thr	AAC .Asn	TGG Trp	CAA Gln	AAG Lys 125	CTT Leu	GAG Glu	383
				AAG Lys												401

## (2) INFORMATION FOR SEQ ID NO: 38:

### (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 133 amino acids

- (B) TYPE: amino acid(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:
- Gln Asn Glu Ile Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala 1 5 10 15
- Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu Leu 20 25 30
- Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly Cys 35 40 45
- Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile Val 50 55 60
- Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu Cys 65 70 75 80
- Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln . 85 90 95
- Phe Lys Glu Lys Val Leu Gly Leu Clu Gln Arg Ala Thr Gln Gln Gln 100 105 110
- Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu Ala 115 120 125

Phe Trp His Lys His 130

- (2) INFORMATION FOR SEQ ID NO: 39:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 401 base pairs
    - (B) TYPE: nucleic acid(C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    (B) CLONE: BR36-20-165
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 3..401
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

WO 94/25601	•	128	PCT/EP94/01323	ţ
TC CAA AAT GAA ATC Gln Asn Glu Ile 1	TGC TTG ACA Cys Leu Thr 5	CAC CCC ATC ACA His Pro Ile Thr	AAA TAC ATC ATG 4 Lys Tyr Ile Met 15	17
GCA TGC ATG TCA GC Ala Cys Met Ser Ala 2	a Asp Leu Glu	A GTA ACC ACC AG A Val Thr Thr Se 25	C ACC TGG GTT TTG gr Thr Trp Val Leu	95
CTT GGA GGG GTC CTC Leu Gly Gly Val Leu 35	C GCG GCC CTA 1 Ala Ala Leu	GCG GCC TAC TG Ala Ala Tyr Cy 40	C TTG TCA GTC GGT 14 s Leu Ser Val Gly 45	13
TGT GTT GTG ATT GTG Cys Val Val Ile Val 50	G GGT CAT ATC L Gly His Ile 55	Glu Leu Gly Gl	C AAG CCG GCA ATC 19 y Lys Pro Ala Ile 60	1
GTT CCA GAC AAA GAC Val Pro Asp Lys Glu 65	G GTG TTG TAT 1 Val Leu Tyr 70	CAA CAA TAC GA Gln Gln Tyr Asj 79	p Glu Met Glu Glu	9
TGC TCA CAA GCT GCC Cys Ser Gln Ala Ala 80	CCA TAT ATC Pro Tyr Ile 85	GAA CAA GCT CAG Glu Gln Ala Gli 90	G GTA ATA GCT CAC 28 n Val Ile Ala His 95	7
CAG TTC AAG GAA AAA Gln Phe Lys Glu Lys 100	Val Leu Gly	TTG CTG CAG CG Leu Leu Gln Arg 105	A GCC ACC CAA CAA 33 g Ala Thr Gln Gln 110	5
CAA GCT GTC ATT GAG Gln Ala Val Ile Glu 115	CCC ATA GTA Pro Ile Val	ACT ACC AAC TGG Thr Thr Asn Trr 120	G CAA AAG CTT GAG 38: O Gln Lys Leu Glu 125	3
GCC TTT TGG CAC AAG Ala Phe Trp His Lys 130			. 40:	1
(A) LENGT	CHARACTERIST H: 133 amino	FICS:		
(D) TOPOL	amino acid OGY: linear			
(ii) MOLECULE T		SEO ID NO: 40.		
Gln Asn Glu Ile Cys			Tyr Ile Met Ala 15.	
Cys Met Ser Ala Asp 20	Leu Glu Val	Thr Thr Ser Thr 25	Trp Val Leu Leu 30	
Gly Gly Val Leu Ala 35	Ala Leu Ala 40	Ala Tyr Cys Leu	Ser Val Gly Cys 45	

•

Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile Val 50 55 60

Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu Cys
65 70 75 80

Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln 85 90 95

Phe Lys Glu Lys Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln Gln 100 105 110

Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu Ala 115 120 125

Phe Trp His Lys His

## (2) INFORMATION FOR SEQ ID NO: 41:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 509 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:
  (B) CLONE: PC-2-1
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 3..509
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

CC ATG AGC ACG	AAT CCT AAA CCT	CAA AGA AAA ACC AAA	AGA AAC ACC	47
Met Ser Thr	Asn Pro Lys Pro	Gln Arg Lys Thr Lys	Arg Asn Thr	
1	5	10	15	

- AAC CGT CGC CCA CAG GAC GTC AAG TTC CCG GGC GGT GGT CAG ATC GTT
  Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val
  20 25 30
- GGC GGA GTT TAC TTG TTG CCG CGC AGG GGC CCT AGG ATG GGT GTG CGC
  Gly Gly Val Tyr Leu Leu Pro Arg-Arg Gly Pro Arg Met Gly Val Arg
  35
  40
  45
- GCG ACT CGG AAG ACT TCG GAA CGG TCG CAA CCC CGT GGA CGG CGT CAG

  Ala Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln

WO 94/25601 PCT/EP94/01323 130 50 55 CCT ATT CCC AAG GCG CGC CAG CCC ACG GGC CGG TCC TGG GGT CAA CCC 239 Pro Ile Pro Lys Ala Arg Gln Pro Thr Gly Arg Ser Trp Gly Gln Pro 70 GGG TAC CCT TGG CCC CTT TAC GCC AAT GAG GGC CTC GGG TGG GCA GGG 287 Gly Tyr Pro Trp Pro Leu Tyr Ala Asn Glu Gly Leu Gly Trp Ala Gly 80 TGG CTG CTC TCC CCT CGA GGC TCT CGG CCT AAT TGG GGC CCC AAT GAC 335 Trp Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp 100 CCC CGG CGA AAA TCG CGT AAT TTG GGT AAG GTC ATC GAT ACC CTA ACG 383 Pro Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr 115 TGC GGA TTC GCC GAT CTC ATG GGG TAT ATC CCG CTC GTA GGC GGC CCC 431 Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro ATT GGG GGC GTC GCA AGG GCT CTC GCA CAC GGT GTG AGG GTC CTT GAG 479 Ile Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu GAC GGG GTA AAC TAT GCA ACA GGG AAT TTA 509 Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu (2) INFORMATION FOR SEQ ID NO: 42: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 169 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42: Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Met Gly Val Arg Ala 35 Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg Gln Pro Thr Gly Arg Ser Trp Gly Gln Pro Gly 65 Tyr Pro Trp Pro Leu Tyr Ala Asn Glu Gly Leu Gly Trp Ala Gly Trp

85 90 <sub>95</sub>

Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp Pro
100 105 110

Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro Ile 130 135 140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 145 150 155 160

Gly Val Asn Tyr Ala Thr Gly Asn Leu 165

- (2) INFORMATION FOR SEQ ID NO:43:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 509 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: CDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    - (B) CLONE: PC-2-6
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 3..509
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

CC ATG AGC ACG AAT CCT AAA CCT CAA AGA AAA ACC AAA AGA AAC ACC
Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr
1 5 10 15

AAC CGT CGC CCA CAG GAC GTC AAG TTC CCG GGC GGT GGT CAG ATC GTT

Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val

20 25 30

GGC GGA GTT TAC TTG TTG CCG CGC AGG GGC CCT AGG ATG GGT GTG CGC

Gly Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Met Gly Val Arg

35

40

45

GCG ACT CGG AAG ACT TCG GAA CGG TCG CAA CCC CGT GGA CGG CGT CAG
Ala Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln
50
55
60

<b>WO</b> 94	1/2560	)1				•		1	32						PCT/	E <b>P94</b> /(	01323
								_									
Pro	ATI Ile	Pro	AAG Lys	GCG	CGC Arg	CAG Gln 70	CCC	ACG Thr	GGC	CGG	TCC Ser 75	TGG	GGT Gly	CAA Gln	CCC		239
Gly	Tyr		TGG Trp		Leu	Tyr				Gly					Gly		287
80					85					90					95		
			TCC														335
			Ser	100					105					110	_		
			Lys 115														383
TGC Cys	GGA Gly	Phe	GCC Ala	GAT Asp	CTC Leu	ATG Met	GGG Gly 135	TAT Tyr	ATC Ile	CCG Pro	CTC Leu	GTA Val 140	GGC Gly	GGC Gly	CCC Pro		431
ATT Ile	GGG Gly 145	GGC Gly	GTC Val	GCA Ala	AGG Arg	GCT Ala 150	CTC Leu	GCA Ala	CAC His	GGT Gly	GTG Val 155	AGG Arg	GTC Val	CTT Leu	GAG Glu		479
			AAC Asn													·	509
(2)	165  (2) INFORMATION FOR SEQ ID NO: 44:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 169 amino acids  (B) TYPE: amino acid  (D) TOPOLOGY: linear																
	(ii)		LECUI														
	(xi)	SE	QUENC	E DI	SCRI	PTIC	N: S	SEQ :	ED NO	): <b>4</b> 4	۱: ·						
Met 1	Ser	Thr	Asn	Pro 5	Lys	Pro	Gln	Arg	Lys 10	Thr	Lys	Arg	Asn	Thr 15	Asn		
Arg	Arg	Pro	Gln 20	Asp	Val	Lys	Phe	Pro 25	Gly	Gly	Gly	Gln	Ile 30	Val	Gly		
Gly	Val	Tyr 35	Leu	Leu	Pro	Arg	Arg 40	Gly	Pro	Arg	Met	Gly 45	Val	Arg	Ala	•	
Thr	Arg 50	Lys	Thr	Ser	Glu	Ar <del>g</del> 55	Ser	Gln	Pro	Arg	Gly 60	Arg	Arg	Gln	Pro		
Ile 65	Pro	Lys	Ala	Arg	Gln 70	Pro	Thr	Gly	Arg	Ser 75	Trp	Gly	Gln	Pro	Gly 80		
Tyr	Pro	Trp	Pro	Leu	Tyr	Ala	Asn	Glu	Gly	Leu	Gly	Trp	Ala	Gly	Trp		

WO 94/25601 PCT/EP94/01323 133 Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp Pro 105 Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys 120 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro Ile Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 155 Gly Val Asn Tyr Ala Thr Gly Asn Leu 165 (2) INFORMATION FOR SEQ ID NO: 45: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 580 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: CDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (vii) IMMEDIATE SOURCE: (B) CLONE: PC-4-1 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 2..580 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45: A ACG TGC GGA TTC GCC GAT CTC ATG GGG TAT ATC CCG CTC GTA GGC 46 Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly GGC CCC ATT GGG GGC GTC GCA AGG GCT CTC GCA CAC GGT GTG AGG GTC 94 Gly Pro Ile Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val 25 CTT GAG GAC GGG GTA AAC TAT GCA ACA GGG AAT TTA CCC GGT TGC TCT 142 Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser 35 TTC TCT ATC TTT ATT CTT GCT CTT-CTC TCG TGT CTG ACC GTT CCG GCC 190

238

Phe Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala

TCT GCA GTT CCC TAC CGA AAT GCC TCT GGG ATT TAT CAT GTT ACC AAT

WO 94	4/256	01				•		1	134						PCT/EP94/0	1323
Ser	Ala 65		Pro	Tyr	Arg	Asn 70	Ala	Ser	Gly	Ile	Tyr 75	His	Val	Thr	Asn	
	Cys		AAC Asn													286
			GGT Gly													334
			CAA Gln 115													382
GTC Val	ACG Thr	GCT Ala 130	CCT Pro	CTT Leu	CGG Arg	AGA Arg	GCC Ala 135	GTT Val	GAC Asp	TAC Tyr	CTA Leu	GCG Ala 140	GGA Gly	GGG Gly	GCT Ala	430
Ala			TCC Ser													478
TTG Leu 160	GTA Val	GGC	CAA Gln	ATG Met	TTC Phe 165	ACC Thr	TAT Tyr	AGG Arg	CCT Pro	CGC Arg 170	CAG Gln	CAC His	GCT Ala	ACG Thr	GTG Val 175	526
			AAC Asn													574
ATG Met																580
(2)		i) S (A (B	EQUE () LE () TY () TO	NCE NGTH PE :	CHAR : 19	ACTE	RIST ino id	ICS :								
			ECUL UENC			_		EQ I	D NO	: 46	·					
Thr 1	Cys	Glý	Phe i	Ala 5	Asp	Leu	Met	Gly	Tyr 10	Ile	Pro	Leu	Val	Gly 15	Gly	
Pro	Ile	Gly	Gly ' 20	Val .	Ala .	Arg .	Ala	Leu 25	Ala	His	Gly	Val	Arg 30	Val	Leu	
Glu	Asp	Gly 35	Val i	Asn '	Tyr .	Ala	Thr -	Gly	Asn	Leu	Pro	Gly 45	Cys	Ser	Phe	
Ser	Ile 50	Phe	Ile 1	Leu :	Ala :	Leu 55	Leu	Ser	Cys	Leu	Thr 60	Val	Pro	Ala	Ser	

Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His 85 90 95

Ala Pro Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys
100 105 110

Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val

Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala 130 135 140

Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln 165 170 175

Asn Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 47:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 580 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
     (B) CLONE: PC-4-6
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..580
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:
- A ACG TGC GGA TTC GCC GAT CTC ATG GGG TAT ATC CCG CTC GTA GGC
  Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly
  1 5 10
- GGC CCC ATT GGG GGC GTC GCA AGG GCT CTC GCA CAC GGT GTG AGG GTC

#### WO 94/25601 PCT/EP94/01323 136 Gly Pro Ile Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val CTT GAG GAC GGG GTA AAC TAT GCA ACA GGG AAT TTA CCC GGT TGC TCT 142 Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser 40 TTC TCT ATC TTT ATT CTT GCT CTT CTC TCG TGT CTG ACC GTT CCG GCC 190 Phe Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala 55 TCT GCA GTT CCC TAC CGA AAT GCC TCT GGG ATT TAT CAT GTT ACC AAT 238 Ser Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn 70 GAT TGC CCA AAC TCT TCC ATA GTC TAT GAG GCA GAT AAC CTG ATC CTA Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu CAC GCA CCT GGT TGC GTG CCT TGT GTC ATG ACA GGT AAT GTG AGT AGA His Ala Pro Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg 100 105 TGC TGG GTC CAA ATT ACC CCT ACA CTG TCA GCC CCG AGC CTC GGA GCA 382 Cys Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala 115 120 GTC ACG GCT CCT CTT CGG AGA GCC GTT GAC TAC CTA GCG GGA GGG GCT 430 Val Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala 130 135 GCC CTC TGC TCC GCG TTA TAC GTA GGA GAC GCG TGT GGG GCA CTA TTC 478 Ala Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe 145 TTG GTA GGC CAA ATG TTC ACC TAT AGG CCT CGC CAG CAC GCT ACG GTG 526 Leu Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val 160 CAG AAC TGC AAC TGT TCC ATT TAC AGT GGC CAT GTT ACC GGC CAC CGG 574 Gln Asn Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg 180 ATG GCA 580 Met Ala

#### (2) INFORMATION FOR SEQ ID NO: 48:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly 5

- Pro Ile Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu
- Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
- Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser
- Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp
- Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His
- Ala Pro Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys 105
- Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val 120
- Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala 135
- Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu 150
- Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln 170
- Asn Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met 180

Ala

- (2) INFORMATION FOR SEQ ID NO: 49:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 959 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE: (B) CLONE: PC-3-4

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 3..959

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

CC	ATG Met 1	AGC Ser	ACG Thr	AAT Asn	CCT Pro 5	AAA Lys	CCT Pro	CAA Gln	AGA Arg	AAA Lys 10	ACC Thr	AAA Lys	AGA Arg	AAC Asn	ACC Thr 15	47
AAC Asn	CG1	CGC Arg	CCA Pro	CAG Glm 20	Asp	GTC Val	Lys	TTC Phe	CCG Pro	Gly	GG1 Gly	GGI Gly	CAG	ATC Ile 30	GTT Val	95
GGC Gly	GGA Gly	GTI Val	TAC Tyr 35	Leu	TTG Leu	CCG	Arg	AGG Arg 40	Gly	CCI Pro	AGG Arg	ATG Met	GGT Gly 45	Val	CGC Arg	143
GCG Ala	ACT	CGG Arg	Lys	ACT	TCG Ser	GAA Glu	CGG Arg	Ser	CAA Gln	CCC Pro	CGT Arg	GGA Gly 60	Arg	CGT	CAG Gln	191
Pro	ATT Ile 65	Pro	AAG Lys	GCG Ala	CGC Arg	CAG Gln 70	CCC	ACG Thr	GGC	CGG	TCC Ser 75	Trp	GGT Gly	CAA Gln	CCC	239
GGG Gly 80	Tyr	CCT Pro	TGG	CCC	CTT Leu 85	TAC Tyr	GCC Ala	AAT Asn	GAG Glu	GGC Gly 90	Leu	GGG	TGG	GCA Ala	GGG Gly 95	287
TGG Trp	CTG Leu	CTC Leu	TCC Ser	CCT Pro 100	CGA Arg	GGC Gly	TCT Ser	CGG Arg	CCT Pro 105	AAT Asn	TGG	GGC Gly	CCC Pro	AAT Asn 110	GAC Asp	335
CCC Pro	CGG Arg	CGA Arg	AAA Lys 115	TCG Ser	CGT Arg	AAT Asn	TTG Leu	GGT Gly 120	AAG Lys	GTC Val	ATC Ile	GAT Asp	ACC Thr 125	CTA Leu	ACG Thr	383
TGC Cys	GGA Gly	TTC Phe 130	GCC Ala	GAT Asp	CTC Leu	ATG Met	GGG Gly 135	TAT Tyr	ATC Ile	CCG Pro	CTC Leu	GTA Val 140	GGC Gly	GGC Gly	CCC Pro	431
ATT Ile	GGG Gly 145	GGC Gly	GTC Val	GCA Ala	AGG Arg	GCT Ala 150	CTC Leu	GCA Ala	CAC His	GGT Gly	GTG Val 155	AGG Arg	GTC Val	CTT Leu	GAG Glu	479
													TCT Ser			527
ATC Ile	TTT Phe	ATT Ile	CTT Leu	GCT Ala 180	CTT Leu	CTC Leu	TCG Ser	TGT Cys	CTG Leu 185	ACC Thr	GTT Val	CCG Pro	GCC Ala	TCT Ser 190	GCA Ala	575
GTT Val	CCC Pro	TAC Tyr	CGA Arg 195	AAT Asn	GCC Ala	TCT Ser	GGG Gly	ATT Ile 200	TAT Tyr	CAT His	GTT Val	ACC Thr	AAT Asn 205	GAT Asp	TGC Cys	623

139

CCA Pro	AAC Asn	TCT Ser 210	TCC Ser	ATA Ile	GTC Val	TAT Tyr	GAG Glu 215	GCA Ala	GAT Asp	AAC Asn	CTG Leu	ATC Ile 220	CTA Leu	CAC His	GCA Ala		671
CCT Pro	GGT Gly 225	TGC Cys	GTG Val	CCT Pro	TGT Cys	GTC Val 230	ATG Met	ACA Thr	GGT Gly	AAT Asn	GTG Val 235	AGT Ser	AGA Arg	TGC Cys	TGG Trp		719
GTC Val 240	CAA Gln	ATT Ile	ACC Thr	CCT Pro	ACA Thr 245	CTG Leu	TCA Ser	GCC Ala	CCG Pro	AGC Ser 250	CTC Leu	GGA Gly	GCA Ala	GTC Val	ACG Thr 255		767
GCT Ala	CCT Pro	CTT Leu	CGG Arg	AGA Arg 260	GCC Ala	GTT Val	GAC Asp	TAC Tyr	CTA Leu 265	GCG Ala	GGA Gly	GGG Gly	GCT Ala	GCC Ala 270	CTC Leu		815
TGC Cys	TCC Ser	GCG Ala	TTA Leu 275	TAC Tyr	GTA Val	GGA Gly	GAC Asp	GCG Ala 280	TGT Cys	GGG Gly	GCA Ala	CTA Leu	TTC Phe 285	TTG Leu	GTA Val		863
GGC Gly	CAA Gln	ATG Met 290	TTC Phe	ACC Thr	TAT Tyr	Arg	CCT Pro 295	CGC Arg	CAG Gln	CAC His	GCT Ala	ACG Thr 300	GTG Val	CAG Gln	AAC Asn	:	911
rgc Cys	AAC Asn 305	TGT Cys	TCC Ser	ATT Ile	Tyr	AGT Ser 310	GGC Gly	CAT His	GTT Val	ACC Thr	GGC Gly 315	CAC His	CGG Arg	ATG Met	GCA Ala	!	959

### (2) INFORMATION FOR SEQ ID NO: 50:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 319 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly 20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Met Gly Val Arg Ala
35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro 50 55 60

Ile Pro Lys Ala Arg Gln Pro Thr Gly Arg Ser Trp Gly Gln Pro Gly 65 70 75 80

Tyr Pro Trp Pro Leu Tyr Ala Asn Glu Gly Leu Gly Trp Ala Gly Trp 85 90 95

140

Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp Pro 100 105 110

Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys 115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro Ile 130 135 140

Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Val 180 185 190

Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp Cys Pro 195 200 205

Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His Ala Pro 210 215 220

Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys Trp Val 225 230 235 240

Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val Thr Ala 245 250 255

Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala Leu Cys 260 265 270

Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu Val Gly 275 280 285

Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln Asn Cys 290 295 300

Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met Ala 305 310 315

- (2) INFORMATION FOR SEQ ID NO: 51:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 959 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:

(B) CLONE: PC-3-8

### (ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 3..959

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

CC	ATG	AGC	ACG	AAT	CCT	AAA	CCT	CAA	AGA	AAA	ACC	AAA	AGA	AAC	ACC	47
	1	ser	Int	Asn	5	гуѕ	PTO	GIN	Arg	Lys 10	Thr	Lys	Arg	Asn	Thr 15	
AA Ası	c CG	r CG	g Pro	A CAC O Gli 20	ı Ası	GTC Val	Lys	TTC Phe	Pro	Gly	GG7 Gly	GG1 Gly	CAC Glr	ATO 11e	GTT Val	95
GG( Gl <sub>3</sub>	GG Gl	A GT y Va:	T TAC L Ty:	r Lei	TTC	CCG Pro	CGC Arg	AGG Arg	Gly	CCI Pro	AGG Arg	ATG Met	GGT Gly 45	Val	CGC Arg	143
GC0 Ala	ACT Thi	CGC Arg	J Lys	G ACI	TCG Ser	GAA Glu	CGG Arg 55	Ser	CAA Gln	CCC Pro	CGT Arg	GGA Gly 60	Arg	CGI	CAG Gln	191
CC1 Pro	ATT Ile	Pro	AAG Lys	GCG Ala	CGC Arg	CAG Gln 70	Pro	ACG Thr	GGC	CGG	TCC Ser 75	Trp	GGT Gly	CAA Gln	CCC	239
GGG Gly 80	Tyr	Pro	Trp	CCC Pro	CTT Leu 85	Tyr	GCC Ala	AAT Asn	GAG Glu	GGC Glý 90	CTC Leu	GGG Gly	TGG Trp	GCA Ala	GGG Gly 95	287
TGG Trp	CTG	Leu	TCC Ser	Pro	Arg	GGC Gly	TCT Ser	CGG Arg	CCT Pro 105	AAT Asn	TGG Trp	GGC Gly	CCC Pro	AAT Asn 110	GAC Asp	335
CCC	CGG Arg	CGA Arg	AAA Lys 115	TCG Ser	CGT Arg	AAT Asn	TTG Leu	GGT Gly 120	AAG Lys	GTC Val	ATC Ile	GAT Asp	ACC Thr 125	CTA Leu	ACG Thr	383
TGC Cys	GGA Gly	TTC Phe 130	GCC Ala	GAT Asp	CTC Leu	ATG Met	GGG Gly 135	TAC Tyr	ATC Ile	CCG Pro	CTC Leu	GTA Val 140	GGC Gly	GGC Gly	CCC Pro	431
GTT Val	GGG Gly 145	GGC Gly	GTC Val	GCA Ala	AGG Arg	GCT Ala 150	CTC Leu	GCA Ala	CAC His	GGT Gly	GTG Val 155	AGG Arg	GTC Val	CTT Leu	GAG Glu	479
GAC Asp 160	GGG Gly	GTA Val	AAC Asn	TAT Tyr	CCA Pro 165	ACA Thr	GGG Gly	AAT Asn	TTA Leu	CCC Pro 170	GGT Gly	TGC Cys	TCT Ser	TTC Phe	TCT Ser 175	527
ATC Ile	TTT Phe	ATT Ile	CTT Leu	GCT Ala 180	CTT Leu	CTC Leu	TCG- Ser	TGT Cys	CTG Leu 185	ACC Thr	GTT Val	CCG Pro	GCC Ala	TCT Ser 190	GCA Ala	575
GTT	ccc	TAC	CGA	AAT	GCC	TCT	GGG	ATT	TAT	CAT	GTT	ACC	AAT	GAT	TGC	623

WO 94/25601 142											PCT/	EP94/01323				
Va.	l Pro	э Тут	195		Ala	Ser	Gly	7 Ile 200		His	Val	Thr	Asn 205	_	Cys	
Pro	A AAC Asi	TCT Ser 210	Ser	ATA Ile	GTC Val	TAT	GAG Glu 215	Ala	GAT Asp	AAC Asn	CTG Leu	ATC Ile 220	Leu	CAC His	GCA Ala	. 671
CCI	GG1 Gly 225	r Cys	GTG Val	CCT	TGT Cys	GTC Val 230	ATG Met	ACA Thr	GGT Gly	AAT Asn	GTG Val 235	Ser	AGA Arg	TGC Cys	TGG Trp	719
GTC Val 240	Gln	ATT	ACC Thr	CCT Pro	ACA Thr 245	CTG Leu	TCA Ser	GCC Ala	CCG Pro	AGC Ser 250	CTC	GGA Gly	GCA Ala	GTC Val	ACG Thr 255	767
GCT Ala	CCT Pro	CTT Leu	CGG Arg	AGA Arg 260	GCC Ala	GTT Val	GAC Asp	TAC Tyr	CTA Leu 265	GCG Ala	GGA Gly	GGG Gly	GCT Ala	GCC Ala 270	CTC Leu	815
TGC Cys	TCC Ser	GCG Ala	TTA Leu 275	TAC Tyr	GTA Val	GGA Gly	GAC Asp	GCG Ala 280	TGT Cys	GGG Gly	GCA Ala	CTA Leu	TTC Phe 285	TTG Leu	GTA Val	863
GGC	CAA Gln	ATG Met 290	TTC Phe	ACC Thr	TAT Tyr	AGG Arg	CCT Pro 295	CGC Arg	CAG Gln	CAC His	GCT Ala	ACG Thr 300	GTG Val	CAG Gln	AAC Asn	911
TGC Cys	AAC Asn 305	TGT Cys	TCC Ser	ATT Ile	TAC Tyr	AGT Ser 310	GGC	CAT His	GTT Val	ACC Thr	GGC Gly 315	CAC His	CGG Arg	ATG Met	GCA Ala	959
(2)			MOI													
<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 319 amino acids</li><li>(B) TYPE: amino acid</li><li>(D) TOPOLOGY: linear</li></ul>																
			ECUL													
Met 1			UENC Asn									Arg	Asn	Thr 15	Asn	
Arg	Arg	Pro	Gln i	Asp	Val	Lys	Phe	Pro 25	Gly	Gly	Gly	Gln	Ile 30	Val	Gly	
Gly	Val	Tyr 35	Leu 1	Leu i	Pro :	Arg .	Arg 40	Gly	Pro	Arg	Met	Gly 45	Val	Arg	Ala	
Thr	Arg 50	Lys	Thr S	Ser (	3lu i	Arg : 55	Ser	Gln	Pro	Arg	Gly 60	Arg	Arg	Gln	Pro	
lle 65	Pro	Lys :	Ala A	Arg (	3ln 1 70	Pro '	Thr (	Gly .	Arg	Ser '	Trp	Gly	Gln	Pro	Gly	

- Tyr Pro Trp Pro Leu Tyr Ala Asn Glu Gly Leu Gly Trp Ala Gly Trp 85 90 95
- Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp Pro 100 105 110
- Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys 115 120 125
- Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro Val 130 135 140
- Gly Gly Val, Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 145 150 155 160
- Gly Val Asn Tyr Pro Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile 165 170 175
- Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Val 180 185 190
- Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp Cys Pro 195 200 205
- Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His Ala Pro 210 215 220
- Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys Trp Val 225 230 235 240
- Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val Thr Ala
  245 250 255
- Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala Leu Cys 260 265 270
- Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu Val Gly 275 280 285
- Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln Asn Cys 290 295 300
- Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met Ala 305 310 315
- (2) INFORMATION FOR SEQ ID NO: 53:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 959 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO

WO 94/25601 . PCT/EP94/01323

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:

(B) CLONE: PC C/E1

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 2..959

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

CCATGAGCAC	GAATCCTAAA	CCTCAAAGAA	AAACCAAAAG	AAACACCAAC	CGTCGCCCAC	60
AGGACGTCAA	GTTCCCGGGC	GGTGGTCAGA	TCGTTGGCGG	AGTTTACTTG	TTGCCGCGCA	120
GGGGCCCTAG	GATGGGTGTG	CGCGCGACTC	GGAAGACTTC	GGAACGGTCG	CAACCCCGTG	180
GACGGCGTCA	GCCTATTCCC	AAGGCGCGCC	AGCCCACGGG	CCGGTCCTGG	GGTCAACCCG	240
GGTACCCTTG	GCCCCTTTAC	GCCAATGAGG	GCCTCGGGTG	GGCAGGGTGG	CTGCTCTCCC	300
CTCGAGGCTC	TCGGCCTAAT	TGGGGCCCCA	ATGACCCCCG	GCGAAAATCG	CGTAATTTGG	360
GTAAGGTCAT	CGATACCCTA	ACGTGCGGAT	TCGCCGATCT	CATGGGGTAY	ATCCCGCTCG	420
TAGGCGGCCC	CRTTGGGGGC	GTCGCAAGGG	CTCTCGCACA	CGGTGTGAGG	GTCCTTGAGG	480
ACGGGGTAAA	CTATSCAACA	GGGAATTTAC	CCGGTTGCTC	TTTCTCTATC	TTTATTCTTG	540
CTCTTCTCTC	GTGTCTGACC	GTTCCGGCCT	CTGCAGTTCC	CTACCGAAAT	GCCTCTGGGA	600
TTTATCATGT	TACCAATGAT	TGCCCAAACT	CTTCCATAGT	CTATGAGGCA	GATAACCTGA	660
TCCTACACGC	ACCTGGTTGC	GTGCCTTGTG	TCATGACAGG	TAATGTGAGT	AGATGCTGGG	720
TCCAAATTAC	CCCTACACTG	TCAGCCCCGA	GCCTCGGAGC	AGTCACGGCT	CCTCTTCGGA	780
GAGCCGTTGA	CTACCTAGCG	GGAGGGGCTG	CCCTCTGCTC	CGCGTTATAC	GTAGGAGACG	840
CGTGTGGGGC	ACTATTCTTG	GTAGGCCAAA	TGTTCACCTA	TAGGCCTCGC	CAGCACGCTA	900
CGGTGCAGAA	CTGCAACTGT	TCCATTTACA	GTGGCCATGT	TACCGGCCAC	CGGATGGCA	959

- (2) INFORMATION FOR SEQ ID NO: 54:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 319 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 10 15

								•							
Arg	g Arg	Pro	Gln 20		Val	Lys	Phe	Pro 25		, Gly	Gly	Gln	Ile 30		Gly
Gly	/ Val	Tyr 35		Leu	Pro	Arg	Arg 40		Pro	Arg	Met	Gly 45		Arg	Ala
Thr	Arg 50		Thr	Ser	Glu	Arg 55		Gln	Pro	Arg	Gly		Arg	Gln	Pro
Ile 65	Pro	Lys	Ala	Arg	Gln 70	Pro	Thr	Gly	Arg	Ser 75		Gly	Gln	Pro	Gly 80
Тух	Pro	Trp	Pro	Leu 85	Tyr	Ala	Asn	Glu	Gly 90		Gly	Trp	Ala	Gly 95	Trp
Leu	Leu	Ser	Pro 100	Arg	Gly	Ser	Arg	Pro 105		Trp	Gly	Pro	Asn 110	Asp	Pro
Arg	Arg	Lys 115	Ser	Arg	Asn	Leu	Gly 120	Lys	Val	Ile	Asp	Thr 125	Leu	Thr	Cys
Gly	Phe 130	Ala	Asp	Leu	Met	Gly 135	Tyr	Ile	Pro	Leu	Val 140	Gly	Gly	Pro	Val
Gly 145	Gly	Val	Ala	Arg	Ala 150	Leu	Ala	His	Gly	Val 155	Arg	Val	Leu	Glu	Asp 160
Gly	Val	Asn	Tyr	Pro 165	Thr	Gly	Asn	Leu	Pro 170	Gly	Cys	Ser	Phe	Ser 175	Ile
Phe	Ile	Leu	Ala 180	Leu	Leu	Ser	Cys	Leu 185	Thr	Val	Pro	Ala	Ser 190	Ala	Val
Pro	Tyr	Arg 195	Asn	Ala	Ser	Gly	Ile 200	Tyr	His	Val	Thr	Asn 205	Asp	Сув	Pro
Asn	Ser 210	Ser	Ile	Val	Tyr	Glu 215	Ala	ĄaĄ	Asn	Leu	Ile 220	Leu	His	Ala	Pro
Gly 225	Cys	Val	Pro	Сув	Val 230	Met	Thr	Gly	Asn	Val 235	Ser	Arg	Cys	Trp	Val 240
Gln	Ile	Thr	Pro	Thr 245	Leu	Ser	Ala	Pro	Ser 250	Leu	Gly	Ala	Val	Thr 255	Ala
Pro	Leu		Arg 260	Ala	Val	Asp	Tyr	Leu 265	Ala	Gly	Gly	Ala	Ala 270	Leu	Cys
Ser	Ala	Leu 275	Tyr	Val	Gly .	Asp	Ala 280	Сув	Gly	Ala	Leu	Phe 285	Leu	Val	Gly
Gln	Met 290	Phe	Thr	Tyr .		Pro 295	Arg	Gln	His	Ala	Thr 300	Val	Gln	Asn	Cys
Asn 305	Cys	Ser	Ile		Ser 310	Gly	His	Val	Thr	Gly 315	His	Arg	Met	Ala	

(2)	INFORMATION	FOR	SEO	$\mathbf{m}$	NO:	55:
-----	-------------	-----	-----	--------------	-----	-----

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 354 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:
  - (B) CLONE: PC-1-37
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..354
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

ACCACCGGAG	CTTCTATCAC	ATACTCCACT	TACGGCAAGT	TCCTTGCTGA	TGGAGGGTGT	60
TCAGGCGGCG	CGCATGACGT	GATCATATGC	GACGAGTGCC	ATTCCCAGGA	CGCCACCACC	120
ATTCTTGGGA	TAGGCACTGT	CCTTGACCAG	GCAGAGACGG	CTGGAGCTAG	GCTCGTCGTC	180
TTGGCCACGG	NCACCCCTCC	CGGCAGTGTG	ACAACGCCCC	ACCCCAACAT	CGAGGAAGTG	240
GCCCTGCCTC	AGGAGGGGGA	GGTTCCCTTC	TACGGCAGAG	CCATTCCCCT	TGCTTTTATA	300
AAGGGTGGTA	GGCATCTCAT	CTTCTGCCAT	TCCAAGAAAA	ATTGTGATGA	ACTC	354

- (2) INFORMATION FOR SEQ ID NO: 56:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 118 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Thr Thr Gly Ala Ser Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala 1 5 10 15

Asp Gly Gly Cys Ser Gly Gly Ala His Asp Val Ile Ile Cys Asp Glu 20 25 30

							147	7					•	CIÆ	/L 7 <del>4</del> /U	LJA
Cys	His	Ser 35	Gln	Asp	Ala	Thr	Thr 40	Ile	Leu	Gly	Ile	Gly 45	Thr	Val	Leu	
Ąsp	Gln 50	Ala	Glu	Thr	Alá	Gly 55	Ala	Arg	Leu	Val	Val	Leu	Ala	Thr	Xaa	
Thr 65	Pro	Pro	Gly	Ser	Val 70	Thr	Thr	Pro	His	Pro 75	Asn	Ile	Glu	Glu	Val 80	
Ala	Leu	Pro	Gln	Glu 85	Gly	Glu	Val	Pro	Phe 90	Tyr	Gly	Arg	Ala	Ile 95	Pro	
Leu	Ala	Phe	Ile 100	Lys	Gly	Gly	Arg	His 105	Leu	Ile	Phe	Cys	His 110	Ser	Lys	
Lys	Asn	Cys 115	Ąap	Glu	Leu											
(2) INFOR	SEQU (A) (B) (C)	ENCE LEN TYP STR	CHA IGTH: PE: 11 LANDE	RACT 354 ucle DNES	ED NO ERIS bas ic a S: s inea	TICS e pa cid ingl	irs									
(ii)	MOLE	CULE	TYP	E: c	DNA											
(iii)	HYPO	THET	ICAL	: NO												
(iii)	ANTI	-sen	SE:	NO										•		
(vii)				URCE PC-1												
(ix)	(A)	NAM		Y: CI N: 1	DS 354	4										
(xi)	SEQUE	ence	DESC	CRIP	rion :	: SEÇ	O ID	NO:	57:							
ACCACCGGA	G CTI	CTAT	CAC	ATAC	TCC	CT 1	racg(	CAAG	T TO	CTT	GCTG#	I TG	SAGG	STGT		60
TCAGGCGGCC	G CG1	TATG	ACGT	GATO	CATA	rgc d	EACG	\GTGC	C AI	TCC	CAGGZ	CGC	CAC	CACC		120
ATTCTTGGG	TAG	GCAC	CTGT	CCTI	rgacc	AG G	CAG	GACG	G CI	GGAG	CTAG	GCT	CGT	CGTC		180
TTGGNCACGG																240
GCCCTGCCTC	AGG	AGGG	GGA	GGTT	CCCT	TC I	'ACGG	NAGA	G CC	ATTO	CCCI	TGC	TTT	ATA		300
AAGGGTGGTA	GGC	ATCI	CAT	CTTC	TGCC	AT T	CCAA	GAAA	а аа	TGTG	ATGA	ACI	T			354

(i) SEQUENCE CHARACTERISTICS:

(2) INFORMATION FOR SEQ ID NO: 58:

- (A) LENGTH: 133 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Thr Thr Gly Ala Ser Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala
1 5 10 15

Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Val Ile Ile Cys Asp Glu 20 25 30

Cys His Ser Gln Asp Ala Thr Thr Ile Leu Gly Ile Gly Thr Val Leu 35 40 45

Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Xaa Thr Xaa 50 55 60

Thr Pro Pro Gly Ser Val Thr Thr Pro His Pro Asn Ile Glu Glu Val 65 70 75 80

Ala Leu Pro Gln Glu Gly Glu Val Pro Phe Tyr Xaa Arg Ala Ile Pro 85 90 95

Leu Ala Phe Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys 100 105 110

Lys Lys Cys Asp Glu Leu Arg Gln Ala Thr Asp Gln Pro Gly Arg Glu 115 120 125

Arg Pro Trp Glu Tyr 130

- (2) INFORMATION FOR SEQ ID NO: 59:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 357 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    (B) CLONE: PC-1-37
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS

#### (B) LOCATION: 1..357

(xi)	SEQUENCE	DESCRIPTION:	SEO	ID	NO:	59.
------	----------	--------------	-----	----	-----	-----

ATGGCTTTCA TGTCTCCGGA CTTGGAGGTC ATTACCANCA CTTGGGTTCT GGTG	GGGGC 60
GTTGTGGCGA CCCTGNCGNC CTACTGCTTG ACGGTGGGTT CGGTAGCCAT AGTCC	GGTAGG 120
ATCATCCTCT CTGGGAAACC TGCCATCATT NCCGATAGGG AGGTATTATA CCAGG	CAATTT 180
GATGAGATGG AGGAGTGCTC GGCCTCGTTG CCCTATATGG ACGAAACACG TNCC	ATTGCC 240
GGACAATTCA AAGAGAAAGT GCTCGGCTTC ATCAGCACGA CCGGCCAGAA GGCTC	GAAACT 300
CTGAAGCCGG CAGCCACGTC TGTGTGGAAC AAGGCTGATC AGTTCTGGNC CACAT	TAC 357

# (2) INFORMATION FOR SEQ ID NO: 60:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 128 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

### (ii) MOLECULE TYPE: protein

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Met Ala Phe Met Ser Pro Asp Leu Glu Val Ile Thr Xaa Thr Trp Val 1 5 10 15

Leu Val Gly Gly Val Val Ala Thr Leu Xaa Xaa Tyr Cys Leu Thr Val 20 25 30

Gly Ser Val Ala Ile Val Gly Arg Ile Ile Leu Ser Gly Lys Pro Ala 35 40 45

Ile Ile Xaa Asp Arg Glu Val Leu Tyr Gln Gln Phe Asp Glu Met Glu
50 55 60

Glu Cys Ser Ala Ser Leu Pro Tyr Met Asp Glu Thr Arg Xaa Ile Ala 65 70 75 80

Gly Gln Phe Lys Glu Lys Val Leu Gly Phe Ile Ser Thr Thr Gly Gln 85 90 95

Lys Ala Glu Thr Leu Lys Pro Ala Ala Thr Ser Val Trp Asn Lys Ala 100 105 110

Asp Gln Phe Trp Xaa Thr Tyr Met Trp Asn Phe Ile Ser Gly Ile Gln
115 120 125

## (2) INFORMATION FOR SEQ ID NO: 61:

# (i) SEQUENCE CHARACTERISTICS:

WO 94/25601 . PCT/EP94/01323

- (A) LENGTH: 357 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:
  - (B) CLONE: PC-1-48
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..357
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

ATGGCTTGCA TGTCTGCGGA CCTGGAGGTC ATTACCANCA CTTGGGTTCT GGTGGGGGGC 60
GTTGTGGCGN CCCTGGCGGC CTACTGCTTG ACGGTGGGTT CGGTAGCCAT AGTCGGTAGG 120
ATCATCCTCT CTGGGAAACC TGCCATCATT CCCGATAGGG AGGCATTATA CCANCAATTT 180
GATGAGATGG AGGAGTGCTC GGCCTCGTTG CCCTATATGG ACGAGACACG TGCCATTGCC 240
GGACAATTCA AAGAGAAAGT GCTCGGCTTC ATCAGCACGA CCGGCCAGAA GGCTGAAACT 300
CTGAAGCCGG CAGCCACGTC TGTGTGGAAC AAGGCTGANC AGTTCTGGGC CACATAC 357

- (2) INFORMATION FOR SEQ ID NO: 62:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 128 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Met Ala Cys Met Ser Ala Asp Leu Glu Val Ile Thr Xaa Thr Trp Val 1 5 10 15

Leu Val Gly Gly Val Val Ala Xaa Leu Ala Ala Tyr Cys Leu Thr Val 20 25 30

Gly Ser Val Ala Ile Val Gly Arg Ile Ile Leu Ser Gly Lys Pro Ala 35 40 45

Ile Ile Pro Asp Arg Glu Ala Leu Tyr Xaa Gln Phe Asp Glu Met Glu 50 55 60 Glu Cys Ser Ala Ser Leu Pro Tyr Met Asp Glu Thr Arg Ala Ile Ala 65 70 75 80

Gly Gln Phe Lys Glu Lys Val Leu Gly Phe Ile Ser Thr Thr Gly Gln 85 90 95

Lys Ala Glu Thr Leu Lys Pro Ala Ala Thr Ser Val Trp Asn Lys Ala 100 105 110

Xaa Gln Phe Trp Ala Thr Tyr Met Trp Asn Phe Ile Ser Gly Ile Gln 115 120 125

- (2) INFORMATION FOR SEQ ID NO: 63:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 28 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr161"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

# ACCGGAGGCC AGGAGAGTGA TCTCCTCC

- (2) INFORMATION FOR SEQ ID NO: 64:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 28 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr162"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

#### GGGCTGCTCT ATCCTCATCG ACGCCATC

28

- (2) INFORMATION FOR SEQ ID NO: 65:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 28 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr163"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

## GCCAGAGGCT CGGAAGGCGA TCAGCGCT

28

- (2) INFORMATION FOR SEQ ID NO: 66:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 28 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr164"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

#### GAGCTGCTCT GTCCTCCTCG ACGCCGCA

28

(2) INFORMATION FOR SEQ ID NO: 67:

- (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 20 base pairs(B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: YES
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: misc\_feature
  - (B) LOCATION: 1..28
  - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr23"
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

#### CTCATGGGGT ACATTCCGCT

20

- (2) INFORMATION FOR SEQ ID NO: 68:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 27 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
    - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr54"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

### CTATTACCAG TTCATCATCA TATCCCA

- (2) INFORMATION FOR SEQ ID NO: 69:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 24 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)

wo	947	EKN1
77.	7414	

PCT/EP94/01323

154	
(iii) HYPOTHETICAL: YES	
(iii) ANTI-SENSE: NO	
<pre>(ix) FEATURE:     (A) NAME/KEY: misc_feature     (B) LOCATION: 128     (D) OTHER INFORMATION: /standard_name= "HCV Primer HCPrl16"</pre>	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:	
TTTTAAATAC ATCATGRCTG YATG	24
(2) INFORMATION FOR SEQ ID NO: 70:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 33 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
(ii) MOLECULE TYPE: DNA (genomic)	
(iii) HYPOTHETICAL: YES	
(iii) ANTI-SENSE: YES	
<pre>(ix) FEATURE:      (A) NAME/KEY: misc_feature      (B) LOCATION: 128      (D) OTHER INFORMATION: /standard_name= "HCV Primer HCPr66"</pre>	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:	
CTATTATTGT ATCCCRCTGA TGAARTTCCA CAT	33
(2) INFORMATION FOR SEQ ID NO: 71:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	

(ix) FEATURE:

(iii) HYPOTHETICAL: YES

(iii) ANTI-SENSE: YES

(A) NAME/KEY: misc\_feature

WO 94/25601

PCT/EP94/01323

155

- (B) LOCATION: 1..28
- (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPril8:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

### ACTAGTCGAC TAYTGATCCR CTATRWARTT CCACAT

36

- (2) INFORMATION FOR SEQ ID NO: 72:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 25 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
    - (iii) HYPOTHETICAL: YES
    - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1...28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr117:
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

# TTTTAAATAC ATCGCRCTGC ATGCA

25

- (2) INFORMATION FOR SEQ ID NO: 73:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 36 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
      - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPrl19:
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

ACTAGTCGAC TARTTGCATA GCCKRTTCAT CCAYTG

(2)	INFORMATION FOR SEQ ID NO: 74:	•	
	(i) SEQUENCE CHARACTERISTICS:		٠.
	(A) LENGTH: 34 base pairs		
	(B) TYPE: nucleic acid		

(ii) MOLECULE TYPE: DNA (genomic)

(C) STRANDEDNESS: single(D) TOPOLOGY: linear

(iii) HYPOTHETICAL: YES

(iii) ANTI-SENSE: NO

#### (ix) FEATURE:

- (A) NAME/KEY: misc\_feature
- (B) LOCATION: 1..28
- (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr131:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

### GGAATTCTAG ACCTCTGGGA YGARAYTGGA ARTG

34

## (2) INFORMATION FOR SEQ ID NO: 75:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 31 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: YES
- (iii) ANTI-SENSE: NO

#### (ix) FEATURE:

- (A) NAME/KEY: misc\_feature
- (B) LOCATION: 1..28
- (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr130:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

## GGAATTCTAG ACGCTAYCAR GCACGTTGYG C

31

## (2) INFORMATION FOR SEQ ID NO: 76:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 23 base pairs
  - (B) TYPE: nucleic acid

PCT/EP94/01323

157

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: YES
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: misc\_feature
  - (B) LOCATION: 1..28
  - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr134:
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

## CATATAGATG CCCACTTCCT ATC

23

- (2) INFORMATION FOR SEQ ID NO: 77:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 16 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FRATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr3:
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

### GTGTGCCAGG ACCATC

- (2) INFORMATION FOR SEQ ID NO: 78:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)

WO 94/25601 PCT/EP94/01323

```
(iii) HYPOTHETICAL: YES
    (iii) ANTI-SENSE: YES
   (ix) FEATURE:
           (A) NAME/KEY: misc_feature
           (B) LOCATION: 1..28
           (D) OTHER INFORMATION: /standard_name= "HCV Primer
                  HCPr4:
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:
GACATGCATG TCATGATGTA
                                                                         20
(2) INFORMATION FOR SEQ ID NO: 79:
     (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 29 base pairs
           (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
   (iii) HYPOTHETICAL: NO
   (iii) ANTI-SENSE: NO
  (ix) FEATURE:
          (A) NAME/KEY: misc feature
          (B) LOCATION: 1..28
          (D) OTHER INFORMATION: /standard_name= "HCV Primer
                 HCPr152:
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:
TACGCCTCTT CTATATCGGT TGGGGCCTG
                                                                        29
(2) INFORMATION FOR SEQ ID NO: 80:
     (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 26 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
```

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: YES
- (iii) ANTI-SENSE: NO

PCT/EP94/01323

159

ix	FEATURE:

- (A) NAME/KEY: misc\_feature
- (B) LOCATION: 1..28
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

## ATGTTGGGTA AGGTCATCGA TACCCT

26

- (2) INFORMATION FOR SEQ ID NO: 81:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 25 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
      - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: misc\_feature
  - (B) LOCATION: 1..28
  - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr41:
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

## CCCGGGAGGT CTCGTAGACC GTGCA

- (2) INFORMATION FOR SEQ ID NO: 82:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 29 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: YES
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..28
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr40:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

CTATTAAAGA TAGAGAAAGA GCAACCGGG

- (2) INFORMATION FOR SEQ ID NO: 83:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 192 to 203 of the V1 region of HCV type 3
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83: Leu Glu Trp Arg Asn Thr Ser Gly Leu Tyr Val Leu 1 5 10
- (2) INFORMATION FOR SEQ ID NO: 84:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 192 to 203 of the V1 region of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:
  - Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val 1 5 10
- (2) INFORMATION FOR SEQ ID NO: 85:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single

WO 94/25601 PCT/EP94/01323 161

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- (viii) POSITION IN PROTEIN:

(B) MAP POSITION: positions 213 to 223 of the V2 region of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Val Tyr Glu Ala Asp Asp Val Ile Leu His Thr

- (2) INFORMATION FOR SEQ ID NO: 86:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 213 to 233 of the V2 region of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Val Tyr Glu Ala Asp Asn Leu Ile Leu His Ala

- (2) INFORMATION FOR SEQ ID NO: 87:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:

(B) MAP POSITION: positions 230 to 242 of the V3 region of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Val Gln Asp Gly Asn Thr Ser Thr Cys Trp Thr Pro Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 88:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 230 to 242 of the V3 region of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Val Met Thr Gly Asn Val Ser Arg Cys Trp Val Gln Ile

- (2) INFORMATION FOR SEQ ID NO: 89:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 248 to 257 of the V4 region of HCV type 3
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

Val Arg Tyr Val Gly Ala Thr Thr Ala Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 90:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

PCT/EP94/01323

- (iii) HYPOTHETICAL: NO

(ii) MOLECULE TYPE: peptide

- (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 248 to 257 of the V4 region of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Ala Pro Ser Leu Gly Ala Val Thr Ala Pro 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 91:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
- (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 294 to 303 of the V5 region of HCV type 3
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Arg Pro Arg Arg His Gln Thr Val Gln Thr 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 92:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 294 to 303 of the V5 region of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

```
Arg Pro Arg Gln His Ala Thr Val Gln Asn
1 5 10
```

- (2) INFORMATION FOR SEQ ID NO: 93:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 9 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptidé
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN PROTEIN:
    - (B) MAP POSITION: positions 70 to 78 of HCV type 5
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Gln Pro Thr Gly Arg Ser Trp Gly Gln 1 5

- (2) INFORMATION FOR SEQ ID NO: 94:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 8 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: BR33 and BR36
  - (viii) POSITION IN PROTEIN:

(B) MAP POSITION: positions 230 to 237 of the V3 region of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Val Gln Asp Gly Asn Thr Ser Thr 1 5

- (2) INFORMATION FOR SEQ ID NO: 95:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 8 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: HD10

- (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 230 to 237 of the V3 region of HCV type 3  $\,$ 
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Val Gln Asp Gly Asn Thr Ser Ala

- (2) INFORMATION FOR SEQ ID NO: 96:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: BR36
  - (viii) POSITION IN PROTEIN:
- (B) MAP POSITION: positions 248 to 257 of the V4 region of HCV type 3
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Val Lys Tyr Val Gly Ala Thr Thr Ala Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 97:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: BR36

- (viii) POSITION IN GENOME:
  - (B) MAP POSITION: Positions 1688 to 1707 of HCV type 3
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Leu Gly Gly Lys Pro Ala Ile Val Pro Asp Lys Glu Val Leu Tyr Gln
1 5 10 15

Gln Tyr Asp Glu

- (2) INFORMATION FOR SEQ ID NO: 98:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: HD10
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1688 to 1707 of HCV type 3
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Leu Gly Gly Lys Pro Ala Leu Val Pro Asp Lys Glu Val Leu Tyr Gln

1 10 15

Gln Tyr Asp Glu 20

- (2) INFORMATION FOR SEQ ID NO: 99:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1712 to 1731
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln 1 5 10 15

Phe Lys Glu Lys

- (2) INFORMATION FOR SEQ ID NO: 100:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: BR36
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1724 to 1743 of HCV type 3
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Ile Ala His Gln Phe Lys Glu Lys Val Leu Gly Leu Leu Gln Arg Ala 1 5 10 15

Thr Gln Gln Gln

- (2) INFORMATION FOR SEQ ID NO: 101:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (C) INDIVIDUAL ISOLATE: HD10
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1724 to 1743 of HCV type 3
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Ile Ala His Gln Phe Lys Glu Lys Ile Leu Gly Leu Leu Gln Arg Ala

1 5 10 15

Thr Gln Gln Gln 20

- (2) INFORMATION FOR SEQ ID NO: 102:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1688 to 1707 of HCV type 5
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Ala Leu Tyr Gln

1 10 15

Gln Phe Asp Glu 20

- (2) INFORMATION FOR SEQ ID NO: 103:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1688 to 1707
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln

1 15

Gln Phe Asp Glu 20

- (2) INFORMATION FOR SEQ ID NO: 104:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- (viii) POSITION IN GENOME:
  - (B) MAP POSITION: position 1712 to 1731 of HCV type 5
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Ser Ala Ser Leu Pro Tyr Met Asp Glu Thr Arg Ala Ile Ala Gly Gln
1 5 10 15

Phe Lys Glu Lys 20

- (2) INFORMATION FOR SEQ ID NO: 105:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 20 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (viii) POSITION IN GENOME:
    - (B) MAP POSITION: positions 1724 to 1743 of HCV type 5
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Ile Ala Gly Gln Phe Lys Glu Lys Val Leu Gly Phe Ile Ser Thr Thr

1 10 15

Gly Gln Lys Ala 20

- (2) INFORMATION FOR SEQ ID NO: 106:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO

WO 94/25601 PCT/EP94/01323

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:

(B) CLONE: GB48-3-10

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 2..340

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

C TCC ACT GTA ACC GAA AAG GAC ATC AGG GTC GAG GAG GAG GTC TAT

Ser Thr Val Thr Glu Lys Asp Ile Arg Val Glu Glu Glu Val Tyr

1 5 10 15

CAG TGT TGT GAC CTG GAG CCC GAA GCC CGC AAG GCA ATT ACC GCC CTA

Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Ala Ile Thr Ala Leu

20 25 30

ACA GAG AGA CTC TAC GTG GGC GGT CCC ATG CAT ANG ACG ANG GCA ATG

ACA GAG AGA CTC TAC GTG GGC GGT CCC ATG CAT AAC AGC AAG GGA GAC

Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp

35

40

45

CTG TGC GGG TAT CGC AGA TGT CGC GCA AGC GGC GTC TAC ACC ACC AGC

Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser

50 55 60

TTC GGG AAC ACA CTG ACG TGC TAC CTC AAA GCC TCA GCC GCT ATC AAA

Phe Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Lys

65

70

75

GCG GCG GGG CTG AGA GAC TGC ACC ATG TTG GTC TGT GGT GAT GAC CTG
Ala Ala Gly Leu Arg Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu
80 85 90 95

GTT GTC ATC GCT GAG AGC GAT GGC GTA GAG GAG GAC AAA CGA CCC CTC

Val Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Lys Arg Pro Leu

100 105 110

GGA GCC Gly Ala

- (2) INFORMATION FOR SEQ ID NO: 107:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 113 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Ser Thr Val Thr Glu Lys Asp Ile Arg Val Glu Glu Glu Val Tyr Gln
1 5 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Ala Ile Thr Ala Leu Thr 20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp Leu
35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 55 60

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Lys Ala 65 70 75 80

Ala Gly Leu Arg Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Lys Arg Pro Leu Gly
100 105 110

Ala

- (2) INFORMATION FOR SEQ ID NO: 108:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    - (B) CLONE: GB116-3-5
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..340
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

C TCC	ACT	GTA	ACC	GAA	AAG	GAC	ATC	AGG	GTC	GAG	GAG	GAG	GTA	TAT	46
Ser	Thr	Val	Thr	Glu	Lys	Asp	Ile	Arg	Val	Glu	Glu	Glu	Val	Tyr	
1				5				_	10					15	

CAG TGT TGT GAC CTG GAG CCC GAG GCC CGC AGA GCA ATT ACC GCC CTA

Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Arg Ala Ile Thr Ala Leu

20 25 30

ACA GAG AGA CTC TAC GTG GGC GGT CCC ATG CAT AAC AGC AGG GGA GAC

Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Arg Gly Asp

35

40

45

WO 94/2	2560	1								•					PCT/EP9	4/01323
									72							
CTG 1	rgc	GGG	TAT	CGC	AGA	TGC	CGT	GCG	AGC	GGC	GTC	TAC	ACC	ACC	AGC	190
Leu (	-ys	21A	Tyr	Arg	Arg	Сув	Arg 55		ser	GIY	vai	17x	Thr	Thṛ	Ser	
TTC C																238
Phe G	65 51y	ASI	Thr	Leu	Thr	Cys 70	тут	Leu	Lys	Ala	Ser 75	Ala	Ala	Ile	Arg	•
	•					,,					,,					
GCG G																286
Ala A	lla	Gly	Leu	Arg		Cys	Thr	Met	Leu		_	Gly	Asp	Asp	Leu	
80					85					90					95	
GTC G	TC	ATT	GCT	GAA	AGC	GAT	GGC	GTA	GAG	GAG	GAC	AAA	CGA	GCC	CTC	334
Val V	al	Ile	Ala	Glu	Ser	Asp	Gly	Val	Glu	Glu	Asp	Lys	Arg	Ala	Leu	
				100					105					110		
GGA G	CC															340
Gly A	la															340
(2) I	NFO	RMA1	CION	FOR	SEQ	ID I	. OF	109:					•			
•	(						_	rics: ació								
					amiı			acic	18							
					OGY:											
,	221	MOT	-				_ <b>.</b>									
	11)	MOI	IBC01	16 T.	YPE:	pro	ein									
(:	xi)	SEÇ	UENC	E D	ESCR	PTIC	)N: :	SEQ I	D NO	): 10	9:					
Ser T	hr 1	(7=1 <sup>°</sup>	Th.∽	G1	T 120	7.00	71.	3	11- 1	<b>~1</b>	<b>a</b> 1	<b>~</b> 3		_		
Ser T	***	val	1111	5	гåя	Asp	TTE	Arg	10	GIU	GIU	GIU	vaı	Tyr 15	Gln	
Cys C	ys i	Asp		Glu	Pro	Glu	Ala		Arg	Ala	Ile	Thr		Leu	Thr	
			20					25					30			
Glu A	rg 1	Leu	Tyr	Val	Gly	Gly	Pro	Met	His	Asn	Ser	Arg	Glv	Asp	Leu	
		35			-	•	40					45	,			
Crea C	) <i>,</i>	<b>~</b>	<b>3</b>	<b>.</b>	<b>~</b>	<b>3</b>					_			_		
Cys G	50	ıyı	AIG	Arg	cys	<b>Arg</b> 55	Ala	ser	GIŸ	Val	Tyr 60	Thr	Thr	Ser	Phe	
Gly A	sn ?	Thr	Leu	Thr		Tyr	Leu	Lys	Ala	Ser	Ala	Ala	Ile	Arg	Ala	
65					70					75					80	
Ala G	ly I	Leu .	Arg	Asp	Cys	Thr	Met	Leu	Val	Cvs	Glv	Asp	Asp	Leu	Val .	
	-		-	85	-				90	-,-	,		<b>-</b> -	95		
77-3 -3	۱		<b>~</b> 3.		•		••-			_					_	
Val II	re A		Glu 100	ser	Asp	GIY	val	Glu 105	Glu	Asp	Lys	Arg		Leu	Gly	
			_55					203					110			
Ala "																

(2) INFORMATION FOR SEQ ID NO: 110:

PCT/EP94/01323

									1/3							
	(	i) S	(A) (B) (C)	nce Leng Type Strai	TH: : nu NDED	340 ) clei NESS	base c ac : si	pai: id ngle	rs							
	(i:	i) M	OLEC	ULE :	TYPE	: cDi	NA									•
	(ii:	i) H	YPOT	HETIC	CAL:	NO										
	(ii:	i) Al	NTI-	sensi	3: NO	)										
	(vi			iate Clone			3-8									
	(i)			RE: NAME/ LOCAT												
	(xi	.) SE	QUEN	ice d	ESCR	IPTI	ON:	SEQ	ID N	io: 1	.10:					
C T	CC A er T	CT C	TA A Val 1	CC G	AA A lu L 5	AA G	AC A sp I	TC A	ucg G	TC G al G	AG G	AG G lu G	AG G lu V	al T	AT Yr 15	46
CAG Gln	TGT Cys	TG1 Cys	GAC Asp	CTG Leu 20	GAG Glu	CCC	GAA Glu	GCC Ala	CGC Arg	Lys	GTA Val	ATT	ACC Thr	GCC Ala 30	CTA Leu	94
ACA Thr	GAG Glu	AGA Arg	CTC Leu 35	Tyr	GTG Val	GGC	GGT Gly	CCC Pro 40	ATG Met	CAT His	AAT Asn	AGC	AAA Lys 45	GGA Gly	GAC	142
CTG Leu	TGC Cys	GGG Gly 50	Tyr	CGC Arg	AGA Arg	TGC Cys	CGC Arg 55	GCA Ala	AGC Ser	GGC Gly	GTC Val	TAC Tyr 60	ACC Thr	ACC Thr	AGC Ser	190
TTC Phe	GGG Gly 65	AAC Asn	ACA Thr	CTG Leu	ACG Thr	TGC Cys 70	TAT Tyr	CTC Leu	AAA Lys	GCC Ala	TCA Ser 75	GCC Ala	GCC Ala	ATC Ile	AGG Arg	238
GCG Ala 80	TCA Ser	GGG Gly	CTG Leu	AGA Arg	GAC Asp 85	TGC Cys	ACT Thr	ATG Met	CTG Leu	GTC Val 90	TAT Tyr	GGT Gly	GAC Asp	GAC Asp	CTG Leu 95	286
GTC <sup>.</sup> Val	GTC Val	ATT Ile	GCC Ala	GAG Glu 100	AGC Ser	GAT Asp	GGC Gly	GTA Val	GAG Glu 105	GAG Glu	GAC Asp	AAA Lys	CGA Arg	GCC Ala 110	CTC Leu	334
GGA Gly						•										340

(2) INFORMATION FOR SEQ ID NO: 111:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Ser Thr Val Thr Glu Lys Asp Ile Arg Val Glu Glu Glu Val Tyr Gln

1 5 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Thr Ala Leu Thr 20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp Leu 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 60

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg Ala 65 70 75 80

Ser Gly Leu Arg Asp Cys Thr Met Leu Val Tyr Gly Asp Asp Leu Val 85 90 95

Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Lys Arg Ala Leu Gly
100 105 110

Val

- (2) INFORMATION FOR SEQ ID NO: 112:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    - (B) CLONE: GB358-3-3
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..340
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:
- C TCC ACT GTA ACC GAA AAG GAC ATC AGG GTC GAG GAG GAG GTG TAT

VO 94	1/256	01				•	•								PCT/	EP94/01323
									175							
5	er :	rnr	Val 1	chr G	51u I 5	ys A	.sp	lle i	Arg V	7al (	Slu G	lu G	lu V	al I	yr 15	
CAG Gln	TG: Cys	r TG:	r gac s Asp	CTG Leu 20	Glu	CCC Pro	GA0	G GCC	C CGC A Arg 25	Lys	GCA Ala	ATT	ACT Thr	GCC Ala		. 94
ACA Thr	GA0	AGA	CTC J Leu 35	Tyr	GTG Val	GGC	GG1 Gly	CCC Pro	Met	CAT His	AAC Asn	AGC Ser	AAG Lys 45	Gly	GAC Asp	142
CTG Leu	TG1 Cys	GGC Gly 50	TAT Tyr	CGC Arg	AGA Arg	TGC Cys	CGC Arg	Ala	AGC Ser	GGC	GTC Val	TAC Tyr 60	ACC	ACC	AGC Ser	190
TTC Phe	GGG Gly 65	Asn	ACA Thr	CTG Leu	ACG Thr	TGC Cys 70	TAC	Leu	AAA Lys	GCC	TCA Ser 75	GCC Ala	GCT Ala	ATC Ile	AGA Arg	236
GCG Ala 80	GCG Ala	GGG	CTG Leu	AGA Arg	GAC Asp 85	TGC Cys	ACC	ATG Met	TTG Leu	GTC Val 90	TGT Cys	GGT Gly	GAT Asp	GAC Asp	CTG Leu 95	286
GTC Val	GTC Val	ATC	GCT Ala	GAG Glu 100	AGC Ser	GAT Asp	GGC Gly	GTT Val	GAG Glu 105	GAG Glu	GAC Asp	AAA Lys	CGA Arg	GCC Ala 110	CTC Leu	<sup>′</sup> 334
GGA Gly																340
(2)		(i) .	TION SEQUI A) LI	INCE	CHAI	LACTE	RIS'	TICS								
	•	-	B) TY													
			LECUI													
Ser			QUENC Thr									Gl.,	17-1	The same	G1=	
1				5	_,,	-wp		æg	10	GIU	GIU	GIU	val	15	GIN	
Cys	Cys	Asp	Leu 20	Glu	Pro	Glu	Ala	Arg 25	Lys	Ala	Ile	Thr	Ala 30	Leu	Thr	
Glu .	Arg	Leu 35	Tyr	Val	Gly	Gly	Pro 40	Met	His	Asn	Ser	Lys 45	Gly	<b>As</b> p	Leu	
Cys (	Gly 50	Tyr	Arg	Arg	Cys	Arg . 55	Ala	Ser	Gly	Val	Tyr 60	Thr	Thr	Ser	Phe	
3ly 2 65	Asn	Thr	Leu	Thr	Cys 70`	Tyr :	Leu	Lys	Ala	Ser 75	Ala	Ala	Ile	Arg	Ala 80	

WO 94/25601 PCT/EP94/01323 176

Ala Gly Leu Arg Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val

Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Lys Arg Ala Leu Gly 100 105

Ala

### (2) INFORMATION FOR SEQ ID NO: 114:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 340 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:

(B) CLONE: GB549-3-6

- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 2..340
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

C TC	CACG	GTG	ACC	GAA	AGG	GAT	ATC	AGG	ACC	GAG	GAA	GAG	ATC	TAC	46
	r Thr														
:	L			5				_	10					15	

- CAG TGC TGC GAC CTG GAG CCC GAA GCC CGC AAG GTG ATA TCC GCC CTA 94 Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ala Leu 25
- ACG GAA AGA CTC TAC GTG GGC GGT CCC ATG TAC AAC TCC AAG GGG GAC 142 Thr Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp
- CTA TGC GGG CAA CGG AGG TGC CGC GCA AGC GGG GTC TAC ACC ACC AGC 190 Leu Cys Gly Gln Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser 55
- TTC GGG AAC ACT GTA ACG TGT TAT CTC AAG GCC GTT GCG GCT ACT AGG 238 Phe Gly Asn Thr Val Thr Cys Tyr Leu Lys Ala Val Ala Ala Thr Arg 70
- GCC GCA GGT CTG AAA GGT TGC AGC ATG CTG GTT TGT GGA GAC GAC TTA 286 Ala Ala Gly Leu Lys Gly Cys Ser Met Leu Val Cys Gly Asp Asp Leu 85 90

WO 94/25601 PCT/EP94/01323 GTC GTC ATC TGC GAG AGC GGC GGC GTA GAG GAG GAT GCA AGA GCC CTC Val Val Ile Cys Glu Ser Gly Gly Val Glu Glu Asp Ala Arg Ala Leu 100 CGA GCC

340

(2) INFORMATION FOR SEQ ID NO: 115:

Arg Ala

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Glu Ile Tyr Gln 5

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ala Leu Thr 25

Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp Leu 35

Cys Gly Gln Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe

Gly Asn Thr Val Thr Cys Tyr Leu Lys Ala Val Ala Ala Thr Arg Ala 65

Ala Gly Leu Lys Gly Cys Ser Met Leu Val Cys Gly Asp Asp Leu Val 90

Val Ile Cys Glu Ser Gly Gly Val Glu Glu Asp Ala Arg Ala Leu Arg 100 105

Ala

- (2) INFORMATION FOR SEQ ID NO: 116:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO

(vii)	IMME	DIATE :	SOURCE:	
	(B)	CLONE	: GB809-3-1	

#### (ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 2..340

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

CAG TGT TGT GAT CTG GAG CCC GAG GCC CGC AAG GTA ATA GCC GCC CTC         94           Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ala Ala Leu 20         30           ACG GAG AGA CTC TAC GTG GGC GGC CCC ATG CAT AAC AGC AAG GGA GAC Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp 35         142           CTT TGC GGG TAT CGT AGA TGC CGC GCG AGC GGC GTA TAC ACC ACC AGC Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser 50         190           TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg 65         238           GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA ALa Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 90         286           GCT GTG ATC GCC GAG AGC GGT GGC GTT GAG GAC GAC CTC Val Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100         334           GGA GCT         GGA GCT         GAG GCT         GAG GCT	C I	CC A er T	CT G	TG A	CT G hr G	AG A lu A 5	GA G rg A	AC A sp I	TC A le L	AG G ys V	TC G al G 10	AA G	AA G	AA G	TC T	AT yr 15	46
ACG GAG AGA CTC TAC GTG GGC GGC CCC ATG CAT AAC AGC AAG GGA GAC Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp 35 40 45  CTT TGC GGG TAT CGT AGA TGC CGC GCG AGC GGC GTA TAC ACC ACC AGC Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser 50 55 60  TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg 65 70 70 75  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80 85 90 95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT  340	CAG	TGT	TGT	GAT	CTG	GAG	CCC	GAG	GCC	CGC	AAG	GTA	ATA	GCC	GCC	CTC	94
Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp  40  45  CTT TGC GGG TAT CGT AGA TGC CGC GCG AGC GGC GTA TAC ACC ACC AGC Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser  50  TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg  65  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu  80  85  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu  100  GGA GCT  340  GGA GCT	GID	Суз	Cys	Asp		Glu	Pro	Glu	Ala			Val	Ile	Ala			
CTT TGC GGG TAT CGT AGA TGC CGC GCG AGC GGC GTA TAC ACC ACC AGC Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser  50  TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg 65  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80  85  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100  105  GGA GCT  340	ACG	GAG	AGA	CTC	TAC	GTG	GGC	GGC	CCC	ATG	CAT	AAC	AGC	AAG	GGA	GAC	142
CTT TGC GGG TAT CGT AGA TGC CGC GCG AGC GGC GTA TAC ACC ACC AGC Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser 55	Thr	Glu	Arg	Leu	Tyr	Val	Gly	Gly		Met	His	Asn	Ser	Lys	Gly	Asp	
Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser  50  TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg  65  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu  80  85  90  95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu  100  105  110				35					40					45			
Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser  50  TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg  65  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu  80  85  90  95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu  100  105  110	CĻT	TGC	GGG	TAT	CGT	AGA	TGC	CGC	GCG	AGC	GGC	GTA	TAC	ACC	ACC	AGC	190
TTC GGG AAC ACA ATG ACG TGC TAC CTT AAG GCC TCA GCA GCC ATC AGG Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg 65  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80  85  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100  105  110  GGA GCT  340	Leu	Cys	Gly	Tyr	Arg	Arg	Суз	Arg	Ala	Ser	Gly	Val	Tyr	Thr	Thr	Ser	
Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg  65 70 75  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA  Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu  80 85 90 95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC  Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu  100 105 110  GGA GCT			50					55					60				
Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg  65 70 75  GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA  Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu  80 85 90 95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC  Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu  100 105 110  GGA GCT	TTC	GGG	AAC	ACA	ATG	ACG	TGC	TAC	CTT	AAG	GCC	TCA	GCA	GCC	ATC	AGG	239
GCT GCG GGG CTA AAG GAT TGC ACC ATG CTG GTT TGC GGT GAC GAC CTA Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100  GGA GCT  340	Phe	Gly	Asn	Thr	Met	Thr	Cys	Tyr	Leu	Lys	Ala	Ser	Ala	Ala	Ile	Arg	236
Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80 85 90 95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT		65														_	
Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80 85 90 95  GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT	GCT	GCG	GGG	CTA	AAG	GAT	TGC	ACC	ATG	CTG	بلبلت	TCC	CCT	GNC	CAC	Cma	206
GTC GTG ATC GCC GAG AGC GGT GGC GTT GAG GAG GAC AAA CGA GCC CTC Val Val Ile Ala Glu Ser Gly Gly Val Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT	Ala	Ala	Gly	Leu	Lys	Asp	Сув	Thr	Met	Leu	Val	Cys	Glv	Asp	Asp	Leu	286
Val Val Ile Ala Glu Ser Gly Gly Val Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT 340	80											•	•				
Val Val Ile Ala Glu Ser Gly Gly Val Glu Asp Lys Arg Ala Leu 100 105 110  GGA GCT 340	GTC	GTG	ATC	GCC	GAG	»GC	CCT	ccc	· CTIT	CD C	~~~	~~~					
100 105 110 GGA GCT 340	Val	Val	Ile	Ala	Glu	Ser	Glv	Glv	Val	Glu	GAG	Agn	AAA	CGA	GCC	CTC	334
GGA GCT					100		2	,			-	nsp	шуз	ALG		Ten	
340	CC2																
Gly Ala																	340

## (2) INFORMATION FOR SEQ ID NO: 117:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Ser Thr Val Thr Glu Arg Asp Ile Lys Val Glu Glu Glu Val Tyr Gln 1 5 15

WO 94/25601 PCT/EP94/01323 179 Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ala Ala Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe Gly Asn Thr Met Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu Gly 105 Ala (2) INFORMATION FOR SEQ ID NO: 118: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 574 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (vii) IMMEDIATE SOURCE: (B) CLONE: GB358-4-1 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1..574 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118: ACT TGC GGC TTT GCC GAC CTC ATG GGA TAC ATC CCG CTC GTA GGC GCC 48 Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

CCT GTG GGT GGC GTC GCC AGG GCC CTG GCA CAC GGT GTT AGG GCT GTG

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

GAG GAC GGG ATC AAT TAT GCG ACA GGG AAT CTT CCC GGT TGC TCT TTC Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe

35

96

WO 94	/2560	1													PCT/EI	94/01323
								18	0			,				_
	ATC															192
Ser	Ile	Phe	Leu	Leu	Ala		Leu	Ser	Cys	Leu		Val	Pro	Thr	Ser	
	50					55					60					
	GTC															240
	Val	Asn	Tyr	Arg	Asn	Ala	Ser	Gly	Ile	Tyr	His	Ile	Thr	Asn	Asp	
65					70					75		٠			80	
TGC	CCG	AAC	TCG	AGC	ATA	GTG	TAC	GAG	ACC	GAG	CAC	CAC	ATC	CTA	CAC	288
Cys	Pro	Asn	Ser	Ser	Ile	Val	Tyr	Glu	Thr	Glu	His	His	Ile	Leu	His	
				85					90					95		
	CCA															336
Leu	Pro	Gly		Leu	Pro	Cys	Val	Arg	Val	Gly	Asn	Gln	Ser	Arg	Cys	
			100					105					110			
	GTG															384
Trp	Val		Leu	Thr	Pro	Thr		Ala	Ala	Pro	Tyr	Ile	Gly	Ala	Pro	
		115					120					125				
	GAA															432
Leu	Glu	Ser	Leu	Arg	Ser		Val	Asp	Leu	Met	Val	Gly	Ala	Ala	Thr	
	130					135		٠			140					
	TGC															480
	Cys	Ser	Ala	Leu		Ile	Gly	Asp	Leu		Gly	Gly	Val	Phe	Leu	
145					150					155					160	
GTT	GGT	CAG	ATG	TTC	TCT	TTC	CAG	CCG	CGG	CGC	CAC	TGG	ACT	ACG	CAG	528
Val	Gly	Gln	Met	Phe	Ser	Phe	Gln	Pro	Arg	Arg	His	Trp	Thr	Thr	Gln	
				165					170					175		
	TGC														A	574
Asp	СЛа	Asn		Ser	Ile	Tyr	Ala	Gly	His	Val	Thr	Gly	His	Arg		
			180					185					190			
(2)	INFO	RMAT	'ION	FOR	SEQ	ID N	TO: 1	19:								

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 191 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 10

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Thr Ser

50 55 60

Ala Val Asn Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Glu His His Ile Leu His
85 90 95

Leu Pro Gly Cys Leu Pro Cys Val Arg Val Gly Asn Gln Ser Arg Cys
100 105 110

Trp Val Ala Leu Thr Pro Thr Val Ala Ala Pro Tyr Ile Gly Ala Pro 115 120 125

Leu Glu Ser Leu Arg Ser His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Ala Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Ser Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Val Thr Gly His Arg 180 185 190

- (2) INFORMATION FOR SEQ ID NO: 120:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 574 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (vii) IMMEDIATE SOURCE:
    (B) CLONE: GB549-4-3
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..574
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

ACG TGC GGC TTT GCC GAC CTC ATG GGA TAC ATC CCG CTC GTG GGC GCC

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

CCT GTG GGT GGC GTC GCC AGG GCC TTG GCA CAT GGT GTC AGG GCC GTG

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

20 25 30

WO 94/25601 . PCT/EP94/01323

GAG	GAC	GGG	ATT	AAC	TAT	GCA	ACA	GGG	AAT	CIT	ccc	GGT	TGC	TCC	TTT		144
		35					40					45	_				
TCT	ATC	TTC	CTT	CTA	GCA	CTT	CTC	TCG	TGC	TTG	ACT	GTC	CCG	GCC	TCG	•	192
Ser	Ile 50	Phe	Leu	Leu	Ala	Leu 55	Leu	Ser	Cys	Leu	Thr 60		Pro	Ala	Ser		
GCG	CAG	CAC	TAC	CGG	AAC	ATC	TCG	GGC	ATT	TAT	CAC	GTC	ACC	AAT	GAC		240
Ala	Gln	His	Tyr	Arg	Asn	Ile	Ser	Gly	Ile	Tyr	His	Val	Thr	Asn	Asp		
65					70	•				75					80		
TGC	CCG	AAC	TCT	AGT	ATA	GTG	TAT	GAA	GCT	GAC	CAT	CAT	ATC	ATG	CAT		288
Cys	Pro	Asn	Ser		Ile	Val	Tyr	Glu	Ala	Asp	His	His	Ile	Met	His		
				85					90					95			
CTA	CCA	GGG	TGT	GTG	CCT	TGC	GTG	AGA	ACC	GGG	AAC	ACC	TCG	CGC	TGC		336
Leu	Pro	Gly	Cys	Val	Pro	Cys	Val	Arg	Thr	Gly	Asn	Thr	Ser	Arg	Cys		
			100					105					110				
TGG	GTT	CCT	TTA	ACA	CCC	ACT	GTG	GCT	GCC	CCC	TAT	GTT	GGC	GCG	CCG		384
Trp	Val	Pro	Leu	Thr	Pro	Thr	Val	Ala	Ala	Pro	Tyr	Val	Gly	Ala	Pro		
		115					120	•				125					
CTC	GAA	TCC	ATG	CGG	CGG	CAC	GTG	GAC	TTA	ATG	GTG	GGT	GCC	GCC	ACC		432
Leu	Glu	Ser	Met	Arg	Arg		Val	Asp	Leu	Met	Val	Gly	Ala	Ala	Thr		
	130					135					140						
GTC	TGC	TCG	GCC	CTG	TAC	ATC	GGA	GAC	CTT	TGC	GGA	GGT	GTC	TTC	CTG		480
Val	Сув	Ser	Ala	Leu	Tyr	Ile	Gly	qaA	Leu	Сув	Gly	Gly	Val	Phe	Leu		
145					150					155					160		
GTC	GGG	CAG	ATG	TTC	ACC	TTC	CGG	CCG	CGC	CGC	CAT	TGG	ACT	ACC	CAG		528
Val	Gly	Gln	Met	Phe 165	Thr	Phe	Arg	Pro	Arg 170	Arg	His	Trp	Thr	Thr 175	Gln		
GAC	TGC	AAC	TGC	TCT	ATC	TAT	GAT	GGC	CAC	ATC	ACC	GGC	СЪТ	767	Δ.		574
Asp	Cys	Asn	Cys	Ser	Ile	Tyr	Asp	Gly	His	Ile	Thr	Gly	His	Ara	^		J / 4
			180				_	185				. 4	190	.—3			

# (2) INFORMATION FOR SEQ ID NO: 121:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 191 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30 WO 94/25601

PCT/EP94/01323

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Gln His Tyr Arg Asn Ile Ser Gly Ile Tyr His Val Thr Asn Asp
65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp His His Ile Met His
85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Thr Ser Arg Cys
100 105 110

Trp Val Pro Leu Thr Pro Thr Val Ala Ala Pro Tyr Val Gly Ala Pro 115 120 125

Leu Glu Ser Met Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Val Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Arg Pro Arg Arg His Trp Thr Thr Gln
165 170 175

Asp Cys Asn Cys Ser Ile Tyr Asp Gly His Ile Thr Gly His Arg 180 185 190

# (2) INFORMATION FOR SEQ ID NO: 122:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 574 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (vii) IMMEDIATE SOURCE:

(B) CLONE: GB809-4-3

- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..574
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

ACG TGC GGC TTC GCC GAC CTC ATG GGA TAC ATC CCG CTC GTG GGC GCC

#### WO 94/25601 PCT/EP94/01323 184 Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 10 CCC GTT GGG GGC GTC GCC AGG GCC CTG GCG CAT GGC GTC AGG GCT GTG 96 Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val GAG GAC GGG ATT AAC TAT GCG ACA GGG AAT CTT CCC GGT TGC TCT TTC 144 Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 40 TCT ATC TTC CTC CTG GCA CTT CTT TCG TGC CTC ACT GTC CCA GCG TCA 192 Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser GCT GAG CAC TAC CGG AAT GCT TCG GGC ATC TAT CAC ATC ACC AAT GAC 240 Ala Glu His Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp 75 TGT CCG AAT TCC AGC GTA GTC TAT GAA ACT GAC CAC CAT ATA TTG CAC 288 Cys Pro Asn Ser Ser Val Val Tyr Glu Thr Asp His His Ile Leu His 90 TTG CCG GGG TGC GTA CCC TGC GTG AGG GCC GGG AAC GTG TCT CGT TGC 336 Leu Pro Gly Cys Val Pro Cys Val Arg Ala Gly Asn Val Ser Arg Cys 105 TGG ACG CCG GTA ACA CCT ACG GTG GCT GCC GTA TCC ATG GAC GCT CCG 384 Trp Thr Pro Val Thr Pro Thr Val Ala Ala Val Ser Met Asp Ala Pro 120 CTC GAG TCC TTC CGG CGG CAT GTG GAC CTA ATG GTA GGT GCG GCC ACC 432 Leu Glu Ser Phe Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 135 GTG TGT TCT GTC CTC TAT GTT GGA GAC CTC TGT GGA GGT GCT TTC CTA 480 Val Cys Ser Val Leu Tyr Val Gly Asp Leu Cys Gly Gly Ala Phe Leu 150 GTG GGG CAG ATG TTC ACC TTC CAG CCG CGT CGC CAC TGG ACC ACG CAG 528 Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 GAT TGT AAT TGC TCC ATC TAT ACT GGC CAT ATC ACC GGC CAC AGG A 574 Asp Cys Asn Cys Ser Ile Tyr Thr Gly His Ile Thr Gly His Arg 180 185

# (2) INFORMATION FOR SEQ ID NO: 123:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 191 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Glu His Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Val Val Tyr Glu Thr Asp His His Ile Leu His
85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Ala Gly Asn Val Ser Arg Cys
100 105 110

Trp Thr Pro Val Thr Pro Thr Val Ala Ala Val Ser Met Asp Ala Pro 115 120 125

Leu Glu Ser Phe Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Val Cys Ser Val Leu Tyr Val Gly Asp Leu Cys Gly Gly Ala Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Thr Gly His Ile Thr Gly His Arg 180 185 190

- (2) INFORMATION FOR SEQ ID NO: 124:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 31 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..31
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HCPr206"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

WO 94/25601

PCT/EP94/01323

186

#### TGGGGATCCC GTATGATACC CGCTGCTTTG A

31

- (2) INFORMATION FOR SEQ ID NO: 125:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 30 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: YES
  - (ix) FEATURE:
    - (A) NAME/KEY: misc\_feature
    - (B) LOCATION: 1..30
    - (D) OTHER INFORMATION: /standard\_name= "HCV Primer HcPr207"
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

# GGCGGAATTC CTGGTCATAG CCTCCGTGAA

30

- (2) INFORMATION FOR SEQ ID NO: 126:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB358
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

Val Asn Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 127:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide

- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: Amino acid
  - (C) INDIVIDUAL ISOLATE: GB549
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Gln His Tyr Arg Asn Ile Ser Gly Ile Tyr His Val

- (2) INFORMATION FOR SEQ ID NO: 128:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: Amino acid
    - (C) INDIVIDUAL ISOLATE: GB809
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

Glu His Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 129:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB358
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Val Tyr Glu Thr Glu His His Ile Leu His Leu

1 5 10

(2) INFORMATION FOR SEQ ID NO: 130:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 11 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: amino acid
  - (C) INDIVIDUAL ISOLATE: GB549
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Val Tyr Glu Ala Asp His His Ile Met His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 131:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB809
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

Val Tyr Glu Thr Asp His His Ile Leu His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 132:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB358

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

Val Arg Val Gly Asn Gln Ser Arg Cys Trp Val Ala Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 133:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB549
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

Val Arg Thr Gly Asn Thr Ser Arg Cys Trp Val Pro Leu

5 10

- (2) INFORMATION FOR SEQ ID NO: 134:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB809
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

Val Arg Ala Gly Asn Val Ser Arg Cys Trp Thr Pro Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 135:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino ācids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: peptide /
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: amino acid
  - (C) INDIVIDUAL ISOLATE: GB358
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Ala Pro Tyr Ile Gly Ala Pro Leu Glu Ser
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 136:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB549
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

Ala Pro Tyr Val Gly Ala Pro Leu Glu Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 137:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB809
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Ala Val Ser Met Asp Ala Pro Leu Glu Ser

1 5 10

(2) INFORMATION FOR SEQ ID NO: 138:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 10 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: amino acid
  - (C) INDIVIDUAL ISOLATE: GB358 and GB809
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

Gln Pro Arg Arg His Trp Thr Thr Gln Asp 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 139:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:
    - (A) ORGANISM: amino acid
    - (C) INDIVIDUAL ISOLATE: GB549
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

Arg Pro Arg Arg His Trp Thr Thr Gln Asp 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 140:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (iii) HYPOTHETICAL: NO
  - (vi) ORIGINAL SOURCE:

WO 94/25601

PCT/EP94/01323

192

- (A) ORGANISM: amino acid
- (C) INDIVIDUAL ISOLATE: GB549
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

Arg Pro Arg Arg His Trp Thr Thr Gln Asp 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 141:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 23 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

#### TGGGATATGA TGATGAACTG GTC

23

- (2) INFORMATION FOR SEQ ID NO: 142:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 24 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: YES
    - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

#### CCAGGTACAA CCGAACCAAT TGCC

24

- (2) INFORMATION FOR SEQ ID NO: 143:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 957 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

WO 94/25601 PCT/EP94/01323

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..957

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 1..954

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:

ATG Met	Ser	ACA Thr	AAT Asn	CCI Pro	Lys	CCT Pro	CAA Gln	AGA Arg	Lys 10	Thr	Lys	AGA Arg	AAC Asn	ACT Thr 15	AAC Asn	48
CGC Arg	CGC	CCA Pro	CAG Gln 20	Asp	GTC Val	AAG Lys	TTC Phe	CCG Pro 25	GGC	GGT Gly	GGC	CAG Gln	ATC Ile 30	GTT Val	GGT Gly	96
GGA Gly	GTA Val	TAC Tyr 35	TTG Leu	TTG Leu	CCG Pro	CGC Arg	AGG Arg 40	GGC	CCC	CGG Arg	TTG Leu	GGT Gly 45	GTG Val	CGC Arg	GCG Ala	144
ACG Thr	AGG Arg 50	AAA Lys	ACT Thr	TCC Ser	GAG Glu	CGG Arg 55	TCC Ser	CAG Gln	CCA Pro	CGT Arg	GGG Gly 60	Arg	CGC Arg	CAG Gln	CCC Pro	192
ATC Ile 65	CCC Pro	AAA Lys	GAT Asp	CGG Arg	CGC Arg 70	CCC Pro	ACT Thr	GGC Gly	AAG Lys	TCC Ser 75	TGG Trp	GGA Gly	AAA Lys	CCA Pro	GGA Gly 80	240
TAC Tyr	CCT Pro	TGG Trp	CCC Pro	CTG Leu 85	TAC Tyr	GGG Gly	AAT Asn	GAG Glu	GGC Gly 90	CTC Leu	GGC Gly	TGG Trp	GCA Ala	GGG Gly 95	TGG Trp	288
CTC Leu	CTG Leu	TCC Ser	CCC Pro 100	CGA Arg	GGG Gly	TCT Ser	CGC Arg	CCG Pro 105	TCA Ser	TGG Trp	GGC Gly	CCA Pro	ACT Thr 110	GAC Asp	CCC Pro	336
CGG Arg	CAC His	AGG Arg 115	TCA Ser	CGC Arg	AAC Asn	TTG Leu	GGT Gly 120	AAG Lys	GTC Val	ATC Ile	GAT Asp	ACC Thr 125	CTT Leu	ACG Thr	TGT Cys	384
GGC Gly	TTT Phe 130	GCC Ala	GAC Asp	CTC Leu	Met	GGG Gly 135	TAC Tyr	ATC Ile	CCT Pro	GTC Val	GTC Val 140	GGC Gly	GCC Ala	CCA Pro	GTT Val	432
GGT Gly 145	GGT Gly	GTC Val	GCC Ala	Arg	GCT Ala 150	CTC Leu	GCG Ala	CAT His	Gly	GTG Val 155	AGA Arg	GTT Val	CTG Leu	Glu	GAC Asp 160	480

M	0 %	1/256	)1				•		19	94	-					PCT/EP94/0	1323
									-								
	GGG	Ile	AAC Asn	TAT	GCA Ala 165	Thr	GGG	Asn	Leu	Pro	Gly	TGC	TCC Ser	Phe	TCT Ser 175	ATC Ile	528
				GCC													576
	Phe	Leu	. Leu	Ala 180	Leu	Leu	Ser	Cys	11e 185	Thr	Val	Pro	Val	Ser 190	Gly	Leu	
	CAG	GTC	AAG	AAC	ACC	AGC	AGC	TCT	TAC	ATG	GTA	ACC	AAT	GAC	TGC	CAG	624
	Gln	Val	Lys 195	Asn	Thr	Ser	Ser	Ser 200	Tyr	Met	Val	Thr	Asn 205	Asp	Суз	Gln	
	AAC	AGT	AGC	ATC	GTC	TGG	CAG	CTC	AGG	GAT	GCT	GTT	CTT	CAC	GTC	CCC	672
	Asn	Ser 210	Ser	Ile	Val	Trp	Gln 215	Leu	Arg	<b>A</b> ap	Ala	Val 220	Leu	His	Val	Pro	
	GGG	TGT	GTC	CCT	TGT	GAG	GAG	AAG	GGC	AAC	ATA	TCC	CGC	TGT	TGG	ATA	720
	Gly 225	Cys	Val	Pro	Cys	Glu 230	Glu	Lys	Gly	Asn	Ile 235	Ser	Arg	Суз	Trp		
																240	
	CCG	GTT	TCG	CCC	AAT	ATA	GCT	GTG	AGC	CAA	CCT	GGT	GCG	CTT	ACC	AAG	768
	PIO	vai	ser	Pro	Asn 245	11e	Ala	Val	ser	Gln 250	Pro	Gly	Ala	Leu	Thr 255	Lys	
	GGC	CTG	CGG	ACG	CAT	ATT	GAT	ACC	ATC	ATT	GCA	TCC	GCT	ACG	TTT	TGC	816
	GIÀ	Leu	Arg	Thr 260	His	Ile	Asp	Thr	11e 265	Ile	Ala	Ser	Ala	Thr 270	Phe	Cys	
	TCT	GCC	CTG	TAC	ATA	GGA	GAC	CTG	TGT	GGC	GCG	GTG	ATG	TTG	GCT	TCT	864
	Ser	Ala	Leu 275	Tyr	Ile	Gly	Asp	Leu 280	Сув	Gly	Ala	Val	Met 285	Leu	Ala	Ser	
	CAA	GTC	TTC	ATC	ATC	TCG	CCC	CAG	CAT	CAT	AAG	TTT	GTC	CAG	GAC	TGC	912
•	Gln	Val 290	Phe	Ile	Ile	Ser	Pro 295	Gln	His	His	Lys	Phe 300	Val	Gln	Asp	Cys	
	AAC	TGT	TCC	ATA	TAC	CCA	GGC	CAC	ATC	ACT	GGA	CAT	CGG	ATG	GCG		957
;	Asn 305	Cys	Ser	Ile	Tyr	Pro 310	Gly	His	Ile	Thr	Gly 315	His	Arg	Met	Ala		
	(2)	INFO	RMAT	NOI	FOR	SEQ	ID N	0: 1	44:								
		(	i) s	EQUE	NCE	CHAR	ACTE	RIST	ICS:								
			(A	) LE	ngth	: 31	9 am	ino	acid	s							

- (B) TYPE: amino acid
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly 20 25 30

Gly	Val	Tyr	Leu	Leu	Pro Ar	g Arg	Gly	Pro	Arg	Leu	Gly	Val	Arg	Ala
		35				40					45		-	

- Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro 50 55 60
- Ile Pro Lys Asp Arg Arg Pro Thr Gly Lys Ser Trp Gly Lys Pro Gly
  65 70 75 80
- Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp 85 90 95
- Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
  100 105 110
- Arg His Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
  115 120 125
- Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Val
  130 135 140
- Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 145 150 155 160
- Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile 165 170 175
- Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Val Pro Val Ser Gly Leu 180 185 190
- Gln Val Lys Asn Thr Ser Ser Ser Tyr Met Val Thr Asn Asp Cys Gln
  195 200 205
- Asn Ser Ser Ile Val Trp Gln Leu Arg Asp Ala Val Leu His Val Pro 210 215 220
- Gly Cys Val Pro Cys Glu Glu Lys Gly Asn Ile Ser Arg Cys Trp Ile 225 230 235 240
- Pro Val Ser Pro Asn Ile Ala Val Ser Gln Pro Gly Ala Leu Thr Lys 245 250 255
- Gly Leu Arg Thr His Ile Asp Thr Ile Ile Ala Ser Ala Thr Phe Cys 260 265 270
- Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Ala Val Met Leu Ala Ser 275 280 285
- Gln Val Phe Ile Ile Ser Pro Gln His His Lys Phe Val Gln Asp Cys 290 295 300
- Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met Ala 305 310 315
- (2) INFORMATION FOR SEQ ID NO: 145:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs

(B) TYPE: nucleic acid (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FRATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 2..337

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 2..340

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

C TCA ACG GTC ACG GAG AGG GAC ATC AGA ACT GAG GAG TCC ATA TAC 46 Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Ser Ile Tyr

CTT GCT TGC TCT TTA CCC GAG CAG GCA CGG ACT GCC ATA CAC TCA CTG 94 Leu Ala Cys Ser Leu Pro Glu Gln Ala Arg Thr Ala Ile His Ser Leu

ACT GAG AGG CTT TAC GTG GGA GGG CCC ATG CTA AAC AGC AAA GGG CAA 142 Thr Glu Arg Leu Tyr Val Gly Gly Pro Met Leu Asn Ser Lys Gly Gln

ACC TGC GGA TAC AGA CGC TGC CGC GCC AGC GGA GTG TTC ACC ACT AGC 190 Thr Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser

ATG GGA AAT ACC ATC ACG TGC TAC GTG AAG GCA CAA GCA GCC TGT AAG 238 Met Gly Asn Thr Ile Thr Cys Tyr Val Lys Ala Gln Ala Ala Cys Lys

GCT GCG GGC ATA ATT GCC CCC ACG ATG CTG GTG TGC GGC GAC GAT CTA 286 Ala Ala Gly Ile Ile Ala Pro Thr Met Leu Val Cys Gly Asp Asp Leu 90

GTT GTC ATC TCA GAG AGT CAG GGG ACC GAG GAC GAG CGG AAC CTA 334 Val Val Ile Ser Glu Ser Gln Gly Thr Glu Glu Asp Glu Arg Asn Leu 105

CGA GCC 340 Arg Ala

(2) INFORMATION FOR SEQ ID NO: 146:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 113 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Ser Ile Tyr Leu 1 5 10 15

Ala Cys Ser Leu Pro Glu Gln Ala Arg Thr Ala Ile His Ser Leu Thr 20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met Leu Asn Ser Lys Gly Gln Thr 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser Met 50 55 60

Gly Asn Thr Ile Thr Cys Tyr Val Lys Ala Gln Ala Ala Cys Lys Ala 65 70 75 80

Ala Gly Ile Ile Ala Pro Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ser Glu Ser Gln Gly Thr Glu Glu Asp Glu Arg Asn Leu Arg

Ala

- (2) INFORMATION FOR SEQ ID NO: 147:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 345 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..345
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 1..342
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

ATG AGC ACA CTT CCT AAA CCA CAA AGA AAA ACC AAA AGA AAC ACC AAC

WO 9	4/256	01				•		19	98						PCT/	EP94/01323
Met 1		Thr	Leu	Pro		Pro	Gln	Arg	Lys 10		Lys	Arg	Asn	Thr 15		
		CAC														. 96
Pro	Gly	/ His	Arg 20	Thr	Leu	Ser	Ser	Gln 25		Ala	Val	. Arg	Ser 30		Val	
		ACG Thr	Cys					Ala					Cys			144
TGC Cys	GCA Ala 50	AGA Arg	CTT Leu	CCG Pro	AGC Ser	GGT Gly 55	CGC Arg	AAC Asn	CTC Leu	GCA Ala	GTA Val	Gly	GCC Ala	AAC Asn	CCA Pro	192
TCC Ser 65	Pro	GGG Gly	CGC Arg	GCC Ala	GAA Glu 70	Pro	AGG Arg	GCA Ala	GGT	CCT Pro 75	GGG Gly	CTC Leu	AGC Ser	CCG Pro	GGT Gly 80	240
ACC Thr	CTI	GGC Gly	CCC Pro	TAT Tyr 85	ATG Met	GGA Gly	ATG Met	AGG Arg	GCT Ala 90	GCG Ala	GGT Gly	GGG	CAG Gln	GGT Gly 95	GGC	288
TÇC Ser	TGT Cys	CCC	CGC Arg 100	GCG Ala	GCT Ala	CTC Leu	GCC Ala	CGT Arg 105	CGT Arg	GGG Gly	GCC Ala	CAA Gln	ATG Met 110	ACC Thr	CCC Pro	336
		GGA Gly 115														345
(2)	INF	ORMAT	MOI	FOR	SEQ	ID 1	10: :	148:								
		(E	L) LE	NGTI PE:	I: 1: amir	RACTE 15 am 10 ac 1ine	nino id		-							
	(ii	) MOI	ECUL	E T	PE:	prot	ein				•					
Met 1	(xi) Ser	SEC Thr	UENC Leu	E DE Pro 5	ESCRI Lys	PTIC Pro	N: S Gln	BEQ I	D NO Lys 10	): 14 Thr	l8 : Lys	Arg	Asn	Thr 15	Asn	
Pro	Gly	His	Arg 20	Thr	Leu	Ser	Ser	Gln 25	Ala	Ala	Val	Arg	Ser 30	Leu	Val	•
Glu	Phe	Thr 35	Cys	Tyr	His	Ala	Gly 40	Ala	Pro	Ser	Trp	Val 45	Cys	Val	Gln	•
Cys	Ala 50	Arg	Leu	Pro	Ser	Gly 55	Arg	Asn	Leu	Ala	Val 60	Gly	Ala	Asn	Pro	
Ser 65	Pro	Gly	Arg .	Ala	<b>Glu</b> 70	Pro	Arg	Ala	Gly	Pro 75	Gly	Leu	Ser	Pro	Gly 80	
Thr	Leu	Gly	Pro	Tyr	Met	Gly	Met	Arg	Ala	Ala	Gly	Gly	Gln	Gly	Gly	

85

90

95

Ser Cys Pro Arg Ala Ala Leu Ala Arg Arg Gly Ala Gln Met Thr Pro 100 105 110

Gly Ala Gly 115

- (2) INFORMATION FOR SEQ ID NO: 149:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 280 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: CDNA
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..280
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 2..277
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:
- G GCC TGT GAC CTC AAG GAC GAG GCT AGG AGG GTG ATA ACT TCA CTC
  Ala Cys Asp Leu Lys Asp Glu Ala Arg Arg Val Ile Thr Ser Leu
  1 5 10 15
- ACG GAG CGG CTT TAC TGT GGT GGT CCT ATG TTC AAC AGC AAG GGA CAA
  Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly Gln
  20 25 30
- CAC TGC GGT TAC CGC CGC TGC CGT GCT AGT GGG GTG CTA CCC ACC AGC
  His Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr Ser
  35 40 45
- TTC GGG AAC ACA ATC ACC TGT TAC ATC AAA GCA AAG GCA GCT ACC AAA

  Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Lys Ala Ala Thr Lys

  50 55 60
- GCT GCC GGA ATT AAA AAT CCA TCA TTC CTT GTC TGC GGA GAT GAC TTG
  Ala Ala Gly Ile Lys Asn Pro Ser Phe Leu Val Cys Gly Asp Asp Leu
  65 70 75
- GTC GTG ATT GCT GAG AGT GCA GGG ATC GAT GAG GAC AGA GCG
  Val Val Ile Ala Glu Ser Ala Gly Ile Asp Glu Asp Arg Ala
  80 85 90
- (2) INFORMATION FOR SEQ ID NO: 150:
  - (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 93 amino acids

- (B) TYPE: amino acid
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

Ala Cys Asp Leu Lys Asp Glu Ala Arg Arg Val Ile Thr Ser Leu Thr
1 5 10 15

Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly Gln His 20 25 30

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr Ser Phe 35 40 45

Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Lys Ala Ala Thr Lys Ala
50 55 60

Ala Gly Ile Lys Asn Pro Ser Phe Leu Val Cys Gly Asp Asp Leu Val 65 70 75 80

Val Ile Ala Glu Ser Ala Gly Ile Asp Glu Asp Arg Ala . 85 90

- (2) INFORMATION FOR SEQ ID NO: 151:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 499 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..499
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 1..496
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

ATG AGC ACG AAT CCT AAA CCT CAA AGA AAA ACC AAA AGA AAC ACC AAC

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn

1 5 10 15

CGT CGC CCA CAG GAC GTC AAG TTC CCG GGC GGT GGT CAG ATC GTT GGC 96
Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly
20

WO 94/25601 PCT/EP94/01323

GGA	GTI	TAC	TTG	TTG	CCG	CGC	AGG	GGC	CCT	AGG	ATG	GGT	GTG	CGC	GCG	144
Gly	Val	Tyr	Leu	Leu	Pro	Arg	Arg	Gly	Pro	Arg	Met	Gly	Val	Arg	Ala	
		35					40			•		45				•
ACT	CGG	AAG	ACT	TCG	GAD	CGG	ጥሮር	CAA	ccc	CCT	CCA	ccc	com	~~	CCT	
Thr	Arq	Lvs	Thr	Ser	Glu	Ara	Ser	GJ 22	Dro	y	GGA Glv	7	CGT	CAG	Pro	192
	50					55				9	60	Arg	MY	GIII	PIO	
ATT	CCC	AAG	GCG	CGC	CAG	CCC	ACG	GGC	CGG	TCC	TGG	GGT	CAA	CCC	GGG	240
Ile	Pro	Lys	Ala	Arg		Pro	Thr	Gly	Arg	Ser	Trp	Gly	Gln	Pro	Gly	
65					70					75					80	
TAC	ССТ	TGG	ccc	مليملين	TAC	GCC	አአጥ	CAC	ccc	CTC	CCC	moo.	001			
Tyr	Pro	Trp	Pro	Leu	Tvr	Ala	Asn	Glu	Glv	Ten	GGG	TGG	GCA	GGG	TGG	288
•		•		85	-1-				90	, <b></b>	G <sub>T</sub> y	11p	ALG	95	пр	
CTG	CTC	TCC	CCT	CGA	GGC	TCT	CGG	CCT	AAT	TGG	GGC	CCC	AAT	GAC	ccc	336
Leu	Leu	Ser	Pro	Arg	Gly	Ser			Asn	Trp	Gly	Pro	Asn	Asp	Pro	
			100					105					110			
CGG	CGA	AAA	TCG	CGT	AAT	TALKE.	сст	AAG	GTC	እጥሮ	CAT	200	~mx	3.00	maa	
Arg	Arq	Lys	Ser	Ara	Asn	Leu	Glv	Lvs	Val	Tle	gari	かっと	LOU	Mb~	1GC	384
	-	115					120	-,-	142		-CP	125	пец	1111	Cys	
GGA	TTC	GCC	GAT	CTC	ATG	GGG	TAT	ATC	CCG	CTC	GTA	GGC	GGC	CCC	ATT	432
GIA	Phe 130	Ala	Asp	Leu	Met		Tyr	Ile	Pro	Leu	Val	Gly	Gly	Pro	Ile	
	130					135					140					
GGG	GGC	GTC	GCA	AGG	GCT	CTC	GCA	ሮልሮ	CCT	CTC	»GG	CTC	Collection	CZC	C3.C	
Gly	Gly	Val	Ala	Arg	Ala	Leu	Ala	His	Glv	Val	Ara	Val	Len	GAG	DAC	480
145				_	150				•	155	3				160	
															-	
			TAT			G										499
GTÅ	val	asn	Tyr	Ala 165	Thr											
				703												

# (2) INFORMATION FOR SEQ ID NO: 152:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 166 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly 20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Met Gly Val Arg Ala 35 40 45 WO 94/25601 PCT/EP94/01323

202

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro 55

Ile Pro Lys Ala Arg Gln Pro Thr Gly Arg Ser Trp Gly Gln Pro Gly 70

Tyr Pro Trp Pro Leu Tyr Ala Asn Glu Gly Leu Gly Trp Ala Gly Trp

Leu Leu Ser Pro Arg Gly Ser Arg Pro Asn Trp Gly Pro Asn Asp Pro 105

Arg Arg Lys Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly Pro Ile 135 Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp 145

155

Gly Val Asn Tyr Ala Thr 165

- (2) INFORMATION FOR SEQ ID NO: 153:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 579 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..579
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 1..576
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

ACG TGC GGA TTC GCC GAT CTC ATG GGG TAC ATC CCG CTC GTA GGC GGC 48 Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly 1

CCC GTT GGG GGC GTC GCA AGG GCT-CTC GCA CAC GGT GTG AGG GTC CTT 96 Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu 20

GAG GAC GGG GTA AAC TAT CCA ACA GGG AAT TTA CCC GGT TGC TCT TTC

WO 94/25601

203

Glu Asp Gly Val Asn Tyr Pro Thr Gly Asn Leu Pro Gly Cys Ser Phe
35

40

TCT ATC TTT ATT CTT GCT CTC TCG TGT CTC ACC GCC TCT

TCT ATC TTT ATT CTT GCT CTT CTC TCG TGT CTG ACC GTT CCG GCC TCT

Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser

50 55 60

GCA GTT CCC TAC CGA AAT GCC TCT GGG ATT TAT CAT GTT ACC AAT GAT
Ala Val. Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp
65 70 75 80

TGC CCA AAC TCT TCC ATA GTC TAT GAG GCA GAT AAC CTG ATC CTA CAC

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His

85

90

95

GCA CCT GGT TGC GTG CCT TGT GTC ATG ACA GGT AAT GTG AGT AGA TGC
Ala Pro Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys
100 105 110

TGG GTC CAA ATT ACC CCT ACA CTG TCA GCC CCG AGC CTC GGA GCA GTC
Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val
115
120
125

ACG GCT CCT CGG AGA GCC GTT GAC TAC CTA GCG GGA GGG GCT GCC

Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala

130

135

140

CTC TGC TCC GCG TTA TAC GTA GGA GAC GCG TGT GGG GCA CTA TTC TTG

Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu

145

150

160

GTA GGC CAA ATG TTC ACC TAT AGG CCT CGC CAG CAC GCT ACG GTG CAG
Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln
165 170 175

AAC TGC AAC TGT TCC ATT TAC AGT GGC CAT GTT ACC GGC CAC CGG ATG

Asn Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met

180 185 190

GCG 579

# (2) INFORMATION FOR SEQ ID NO: 154:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D). TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Gly
1 5 10 15

204

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu 20 25 30

Glu Asp Gly Val Asn Tyr Pro Thr Gly Asn Leu Pro Gly Cys Ser Phe
35 40 45

Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp
65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asn Leu Ile Leu His 85 90 95

Ala Pro Gly Cys Val Pro Cys Val Met Thr Gly Asn Val Ser Arg Cys
100 105 110

Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Leu Gly Ala Val 115 120 125

Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Ala Gly Gly Ala Ala 130 135 140

Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln 165 170 175

Asn Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Arg Met
180 185 190

Ala

#### (2) INFORMATION FOR SEQ ID NO: 155:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
    (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..576

ACG	TGC	GGA	TTC	GCC	GAC	CTC	GTG	GGG	TAC	ATC	CCG	CTC	GTA	GGC	GGC	
Thr	Сув	Gly	Phe	Ala	Asp	Leu	Val	Gly	Tyr	Ile	Pro	Leu	Val	Glv	Gly	

1 10 15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

CCC GTT GGG GGC GTC GCA AGG GCT CTC GCA CAT GGT GTG AGG GTT CTT 96 Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu 20

48

GAG GAC GGG GTG AAT TAT GCA ACA GGG AAT CTG CCT GGT TGC TCT TTC 144 Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 40

TCT ATC TTC ATT CTT GCA CTT CTC TCG TGC CTC ACT GTC CCG GCC TCT 192 Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 55

GCA GTT CCC TAC CGA AAT GCC TCT GGG ATC TAT CAT GTC ACC AAT GAT 240 Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp 70

TGC CCA AAC TCT TCC ATA GTC TAT GAG GCA GAT GAT CTG ATC CTA CAC 288 Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Leu Ile Leu His

GCA CCT GGC TGC GTG CCT TGT GTC AGG AAA GAT AAT GTG AGT AGG TGC 336 Ala Pro Gly Cys Val Pro Cys Val Arg Lys Asp Asn Val Ser Arg Cys 105

TGG GTC CAA ATT ACC CCC ACG CTG TCA GCC CCG AGC TTC GGA GCA GTC 384 . Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Phe Gly Ala Val 120 .

ACG GCT CCC CTT CGG AGA GCC GTT GAT TAC TTG GTG GGA GGG GCT GCC 432 Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Val Gly Gly Ala Ala

CTC TGC TCC GCG TTA TAC GTT GGA GAC GCG TGT GGG GCA CTA TTT TTG 480 Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu 155

GTA GGC CAA ATG TTC ACC TAT AGG CCT CGC CAG CAT GCT ACG GTG CAG 528 Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln

GAC TGC AAC TGT TCC ATC TAC AGT GGC CAC GTC ACC GGC CAT CAG ATG 576 Asp Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Gln Met 185

GCA 579 Ala

(2) INFORMATION FOR SEQ ID NO: 156:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

Thr Cys Gly Phe Ala Asp Leu Val Gly Tyr Ile Pro Leu Val Gly Gly
1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu 20 25 30

Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Leu Ile Leu His
85 90 95

Ala Pro Gly Cys Val Pro Cys Val Arg Lys Asp Asn Val Ser Arg Cys
100 105 110

Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Phe Gly Ala Val

Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Val Gly Gly Ala Ala 130 135 140

Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Gln Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 157:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 530 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA

12221		110
(111)	HYPOTHETICAL:	NU

(iii) ANTI-SENSE: NO

## (ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 3..530

#### (ix) FEATURE:

(A) NAME/KEY: mat\_peptide
(B) LOCATION: 3..527

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

CA	CCT Pro 1	ACG Thr	ACA Thr	GCT Ala	CTG Leu 5	CTG Leu	GTG Val	GCC Ala	CAG Gln	TTA Leu 10	CTG Leu	CGG Arg	ATT Ile	CCC Pro	CAA Gln 15	47
GTG Val	GTC Val	ATI Ile	GAC Asp	ATC Ile	Ile	GCA Ala	GGG Gly	AGC Ser	CAC His	Tr	GGG Gly	GTC Val	TTG Leu	TTT Phe	GCC Ala	<b>95</b>
GCC Ala	GCA Ala	TAC	TAT Tyr 35	Ala	TCG Ser	GTG Val	GCT	AAC Asn 40	Trp	ACC	AAG Lys	GTC Val	GTG Val 45	Leu	GTC Val	143
TTG Leu	TTT	CTG Leu 50	Phe	GCA Ala	GGG Gly	GTT Val	GAT Asp 55	Ala	ACT	ACC	CAG Gln	ATT Ile 60	Ser	GGC	GCGC	191
TCC Ser	AGC Ser 65	Ala	CAA Gln	ACG Thr	ACG Thr	TAT Tyr 70	GGC Gly	ATC Ile	GCC Ala	TCA Ser	TTI Phe 75	Ile	ACC Thr	CGC	GGC Gly	239
GCG Ala 80	Gln	CAG Gln	AAA Lys	CTG Leu	CAG Gln 85	ĆTC Leu	ATA Ile	AAT Asn	ACC Thr	AAC Asn 90	Gly	AGC Ser	TGG	CAC His	ATC Ile 95	287
AAC Asn	AGG	ACC Thr	GCC Ala	CTT Leu 100	AAT Asn	TGT Cys	AAT Asn	GAC <b>A</b> sp	AGC Ser 105	CTC	CAG Gln	ACT	GGG Gly	TTC Phe 110	ATA Ile	335
GCC Ala	GGC Gly	CTC Leu	TTC Phe 115	TAC Tyr	TAC Tyr	CAT His	AAG Lys	TTC Phe 120	AAC Asn	TCT Ser	TCT	GGA Gly	TGC Cys 125	CCG Pro	GAT Asp	383
CGG Arg	ATG Met	GCT Ala 130	AGC Ser	TGT Cys	AGG Arg	GCC Ala	CTT Leu 135	GCC Ala	ACT Thr	TTT Phe	GAC Asp	CAG Gln 140	GGC Gly	TGG Trp	GGA Gly	431
ACT Thr	ATC Ile 145	AGC Ser	TAT Tyr	GCC Ala	AAC Asn	ATA Ile 150	TCG Ser	GGT Gly	CCC Pro	AGT Ser	GAT Asp 155	GAC Asp	AAA Lys	CCA Pro	TAT Tyr	479
TGC	TGG	CAC	TAT	CCC	CCA	CGG	CCG	TGC	GGA	GTG	GTG	CCA	GCC	CAA	GAG	527

WO 94/25601 PCT/EP94/01323

208

Cys Trp His Tyr Pro Pro Arg Pro Cys Gly Val Val Pro Ala Gln Glu 160 165 170 175

GTC 530 Val

- (2) INFORMATION FOR SEQ ID NO: 158:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 176 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

Pro Thr Thr Ala Leu Leu Val Ala Gln Leu Leu Arg Ile Pro Gln Val

1 5 10 15

Val Ile Asp Ile Ile Ala Gly Ser His Trp Gly Val Leu Phe Ala Ala 20 25 30

Ala Tyr Tyr Ala Ser Val Ala Asn Trp Thr Lys Val Val Leu Val Leu 35 40 45

Phe Leu Phe Ala Gly Val Asp Ala Thr Thr Gln Ile Ser Gly Gly Ser 50 60

Ser Ala Gln Thr Thr Tyr Gly Ile Ala Ser Phe Ile Thr Arg Gly Ala 65 70 75 80

Gln Gln Lys Leu Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn 85 90 95

Arg Thr Ala Leu Asn Cys Asn Asp Ser Leu Gln Thr Gly Phe Ile Ala 100 105 110

Gly Leu Phe Tyr Tyr His Lys Phe Asn Ser Ser Gly Cys Pro Asp Arg 115 120 125

Met Ala Ser Cys Arg Ala Leu Ala Thr Phe Asp Gln Gly Trp Gly Thr 130 135 140

Ile Ser Tyr Ala Asn Ile Ser Gly Pro Ser Asp Asp Lys Pro Tyr Cys 145 150 155 160

Trp His Tyr Pro Pro Arg Pro Cys Gly Val Val Pro Ala Gln Glu Val
165 170 175

- (2) INFORMATION FOR SEQ ID NO: 159:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single

WO 94/25601 PCT/EP94/01323 209

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS (B) LOCATION: 2..340

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 2..337

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

									et T					TT T. le T		46
															CTC Leu	94
															CAA Gln	142
															AGT Ser	190
ATG Met															AGA Arg	238
GCC Ala 80																286
GTG Val	GCC Ala	ATC Ile	TGC Cys	GAG Glu 100	AGC Ser	CAG Gln	GGG Gly	ACA Thr	CAC His 105	GAG Glu	GAT Asp	GAA Glu	GCA Ala	AGC Ser 110	CTG Leu	334
AGA Arg																340

## (2) INFORMATION FOR SEQ ID NO: 160:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 113 amino acids

(B) TYPE: amino acid

WO 94/25601 PCT/EP94/01323

210

(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

Ser Thr Val Thr Glu His Asp Ile Met Thr Glu Glu Ser Ile Tyr Gln
1 5 10 15

Ser Cys Asp Leu Gln Pro Glu Ala Arg Ala Ile Arg Ser Leu Thr
20 25 30

Gln Arg Leu Tyr Cys Gly Gly Pro Met Tyr Asn Ser Lys Gly Gln Gln 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser Met 50 55 60

Gly Asn Thr Met Thr Cys Tyr Ile Lys Ala Leu Ala Ser Cys Arg Ala 65 70 75 80

Ala Arg Leu Arg Asp Cys Thr Leu Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Ala Ile Cys Glu Ser Gln Gly Thr His Glu Asp Glu Ala Ser Leu Arg 100 105 110

Ala

- (2) INFORMATION FOR SEQ ID NO: 161:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..340
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 2..337
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:
- C TCA ACC GCC ACC GAA CAT GAC ATA TTG ACT GAA GAG TCC ATA TAC Ser Thr Ala Thr Glu His Asp Ile Leu Thr Glu Glu Ser Ile Tyr

VO 9	4/256	01				•		2	11						PCT/	E <b>P</b> 94/01323	
	1				5					10					15		
CA) Gl:	A TC	A TG:	GAC S Asp	TCG Ser 20	Gln	CCC Pro	GAC Asp	GC/ Ala	A CGC A Arg 25	Ala	GCA Ala	ATA Ile	. CGG Arg	TCA Ser 30	CTC Leu	9.	4
ACC	CAA Glr	A CGC	TTG Leu 35	Phe	TGT Cys	GGA Gly	GGC	CCC Pro	) Met	TAT	AAC Asn	AGC Ser	AAG Lys 45	Gly	CAA Gln	14:	2
CAA Gln	TG1 Cys	GGI Gly 50	Tyr	CGC Arg	AGA Arg	TGC Cys	CGC Arg 55	Ala	: AGC	GGC	GTC Val	TTC Phe 60	ACC Thr	ACC Thr	AGT Ser	190	0
ATG Met	GGC Gly 65	Asn	ACC Thr	ATG Met	ACG Thr	TGC Cys 70	TAC Tyr	ATT	'AAG Lys	GCT Ala	TTA Leu 75	GCC Ala	TCC Ser	TGT Cys	AGA Arg	238	3
ACC Thr 80	Ala	GGG Gly	CTC Leu	CGG Arg	GAC Asp 85	TAC	ACG Thr	CTC	CTG Leu	GTG Val 90	TGT Cys	GGT Gly	GAC Asp	GAT Asp	CAT His 95	286	;
GTG Val	GCC	ATC	TGC Cys	GAG Glu 100	AGC Ser	CAG Gln	GGG Gly	ACA Thr	CAC His 105	GAG Glu	GAT Asp	GAA Glu	GCG Ala	AAC Asn 110	CTG Leu	334	k
	GCC Ala															340	,
(2)	(ii)	(i)	TION SEQUE A) LE B) TO C) TO LECUI	ENCE ENGTH (PE: )POLC	CHAI H: 11 amir XGY:	RACTE 13 am 10 ac 1ine	ERIST mino cid car cein	rics aci	ds	): <b>1</b> 6							
Ser 1	Thr	Ala	Thr	Glu 5	His	Asp	Ile	Leu	Thr 10	Glu	Glu	Ser	Ile	Tyr 15	Gln		
Ser	Cys	Asp	Ser 20	Gln	Pro	qaA	Ala	Arg 25	Ala	Ala	Ile	Arg	Ser 30	Leu	Thr		
Gln	Arg	Leu 35	Phe	Сув	Gly	Gly	Pro 40		Tyr	Asn	Ser	Lys 45		Gln	Gln		
Cys	Gly 50	Tyr	Arg	Arg	Cys	Arg 55	Ala	Ser	Gly	Val	Phe 60	Thr	Thr	Ser	Met		
65	Asn	Thr	Met	Thr	Cys 70	Tyr	Ile-	Lys	Ala	Leu 75	Ala	Ser	Cys	Arg	Thr 80		
lla	Gly	Leu	Arg .	Asp 85	Tyr	Thr	Leu	Leu	Val 90	Cys	Gly	Asp .	Asp	His 95	Val		

WO 94/25601

PCT/EP94/01323

212

Ala Ile Cys Glu Ser Gln Gly Thr His Glu Asp Glu Ala Asn Leu Arg 100 105 110

Ala

## (2) INFORMATION FOR SEQ ID NO: 163:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 499 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: CDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..499
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..496
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

ATG A	GC A	CG	AAT	CCT	AAA	CTT	CAA	AGA	AAA	ACC	AAA	CGT	AAC	ACC	AAC	48
Met S	er T	hr	Asn	Pro	Lys	Leu	Gln	Arg	Lys	Thr	Lys	Arg	Asn	Thr	Asn	
1				5					10					15		

- CGC CGC CCC ATG GAC GTT AAG TTC CCG GGT GGT GGC CAG ATC GTT GGC
  Arg Arg Pro Met Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly
  20 25 30
- GGA GTT TAC TTG TTG CCG CGC AGG GGC CCT AGG TTG GGT GTG CGC GCG
  Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala

  35
  40
  45
- ACT CGG AAG ACT TCG GAG CGG TCG CAA CCT CGT GGG AGG CGC CAA CCT
  Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
  50 55 60
- ATC CCC AAG GCG CGC CGA TCC GAG GGC AGA TCC TGG GCG CAG CCC GGG

  Ile Pro Lys Ala Arg Arg Ser Glu Gly Arg Ser Trp Ala Gln Pro Gly
  65 70 75 80
- TAT CCT TGG CCC CTT TAC GGC AAT GAG GGC TGT GGG TGG GCA GGG TGG

  Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp

  85 90 95

CTC CTG TCC CCT CGC GGG TCT CGG CCG TCT TGG GGC CCT AAT GAT CCC 336

WO 94	4/256	01				•			213						PCT/EP9	4/01323
Leu	Leu	. Ser	100		, Gly	Ser	Arg	105		Trp	Gly	Pro	Asn 110	_	Pro	
CGG	CGG	AGG	TCC	: CGC	: AAC	CTG	GGI	AAG	GTC	ATC	GAT	ACC	CTA	ACA	TGC	. 384
Arg	Arg	Arg 115	Ser	Arg	) Asn	Leu	120	. TAR	Val	Ile	Asp	Thr 125	Leu	Thr	Сув	
GGC	TTC	GCC	GAC	CTC	ATG	GGA	TAC	ATC	CCG	CTI	GTA	GGC	GCC	ccc	GTG	432
Gly	Phe	Ala	Asp	Leu	Met	Gly	Tyr	Ile	Pro	Leu	Val	Gly	Ala	Pro	Val	
	130					135					140					
GGT	GGC	GTC	GCC	AGA	GCC	CTG	GCA	CAC	GGT	GTT	AGG	GCT	GTG	GAA	GAC	480
Gly	Gly	Val	Ala	Arg	Ala	Leu	Ala	His	Gly	Val	Arg	Ala	Val	Glu	Asp	
145					150					155					160	
GGG	ATC	AAC	TAC	GCA	ACA	G										499
Gly	Ile	Asn	Tyr	Ala	Thr											
				165												
(2)	INF	ORMA	TION	FOR	SEQ	ID :	NO:	164:								
Met	(xi	() ) MO: ) SE(	D) T LECU QUEN	OPOL LE T CE D Pro	ami: OGY: YPE: ESCR	line prof	ear tein	SEQ :	Lys			Arg	Asn	Thr	Asn	
1	•			5	•	_			10					15		
ALG .	Arg	PIO	20	жър	Val	rys	Pne	25	GIY	GIY	GIÅ	Gln	Ile 30	Val	Gly	
Gly '	Val	Tyr 35	Leu	Leu	Pro	Arg	Arg 40	Gly	Pro	Arg	Leu	Gly 45	Val	Arg	Ala	
Thr .	Arg 50	Lys	Thr	Ser	Glu	Arg 55	Ser	Gln	Pro	Arg	Gly 60	Arg	Arg	Gln	Pro	
Ile :	Pro	Lys	Ala	Arg	Arg	Ser	Glu	Gly	Arg	Ser	Trp	Ala	Gln	Pro	Gly	
65					70					75	-				80	
Tyr :	Pro	Trp	Pro	Leu 85	Tyr	Gly	Asn	Glu	Gly 90	Cys	Gly	Trp	Ala	Gly 95	Trp	
Leu 1	Leu	Ser	Pro 100	Arg	Gly	Ser	Arg	Pro 105	Ser	Trp	Gly	Pro	Asn 110	Asp	Pro	
Arg 1	Arg	Arg 115	Ser	Arg	Asn	Leu	Gly 120		Val	Ile	Asp	Thr 125	Leu	Thr	Cys	
Gly I	Phe 130	Ala	Asp	Leu	Met	Gly 135	Tyr	Ile	Pro	Leu	Val	Gly	Ala	Pro	Val	

WO 94/25601 PCT/EP94/01323

214

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val Glu Asp 145 150 155 160

Gly Ile Asn Tyr Ala Thr 165

## (2) INFORMATION FOR SEQ ID NO: 165:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 499 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

ATGAGCACGA	ATCCTAAACC	TCAAAGAAAA	ACCAAACGTA	ACACCAACCG	CCGCCCTATG	60
GACGTTAAGT	TCCCAGGCGG	TGGTCAGATC	GTTGGCGGAG	TTTACTTGTT	GCCGCGCAGG	120
GGCCCCAGGT	TGGGTGTGCG	CGCGACTCGG	AAGACTTCGG	AGCGGTCGCA	ACCTCGTGGG	180
AGGCGCCAAC	CTATCCCCAA	GGCGCGCCGA	ACCGAGGGCA	GATCCTGGGC	GCAGCCCGGG	240
TATCCTTGGC	CCCTTTACGG	CAATGAGGGC	TGTGGGTGGG	CAGGGTGGCT	CCTGTCCCCT	300
CGCGGNTCTC	GGNCGTCTTG	GGGCCCCAAT	GATCCCCGGN	GGAGATCCCG	CAACTTGGGT	360
AAGGTCATCG	ATACCCTAAC	ATGCGGCTTC	GCCGACCTCA	TGGGATACAT	CCCGCTTGTA	420
GGCGCCCCG	TEGETEGCET	CGCCAGGGCC	CTGGCACATG	GTGTTAGGGC	TGTGGAAGAC	480
GGGATCAATT	ATGCAACAG					499

- (2) INFORMATION FOR SEQ ID NO: 166:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 126 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn

WO 94/25601 . PCT/EP94/01323 215

5 10 15

Arg Arg Pro Met Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly 20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
35 . 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro 50 55 60

Ile Pro Lys Ala Arg Arg Thr Glu Gly Arg Ser Trp Ala Gln Pro Gly 65 70 75 80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp 85 90 95

Leu Leu Ser Pro Arg Xaa Ser Arg Xaa Ser Trp Gly Pro Asn Asp Pro 100 105 110

Arg Xaa Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu
115 120 125

## (2) INFORMATION FOR SEQ ID NO: 167:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..579

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

ACA TGC GGC TTC GCC GAC CTC ATG GGA TAC ATC CCG CTT GTA GGC GCC

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

CCC GTG GGT GGC GTC GCC AGG GCC-CTG GCA CAT GGT GTT AGG GCT GTG

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

20 25 30

GAA GAC GGG ATC AAT TAT GCA ACA GGG AAC CTT CCC GGT TGC TCC TTT 144

WO 94	4/2560	)1													PCT/EF	94/01323
								216	5							
Glu	Asp	Gly 35		Asn	Tyr	Ala	Thr 40		Asn	Leu	Pro	Gly 45	Сув	Ser	Phe	
															TCG	. 192
Ser	Ile 50	Phe	Leu	Leu	Ala	Leu 55	Leu	Ser	Cys	Leu	Thr 60	Val	Pro	Thr	Ser	
	GTT															240
	Val	Asn	Tyr	Arg	Asn	Ala	Ser	Gly	Ile	Tyr	His	Ile	Thr	Asn	Asp	
65					70			•		75					80	
TGC	CCG	AAT	GCA	AGC	ATA	GTG	TAC	GAG	ACC	GAA	AAT	CAC	ATC	TTA	CAC	288
Сув	Pro	Asn	Ala		Ile	Val	Tyr	Glu		Glu	Asn	His	Ile		His	
				85					90					95		
CTC	CCA	GGG	TGC	GTA	CCC	TGT	gtg	AGG	ACT	GGG	AAC	CAG	TCG	CGG	TGT	336
Leu	Pro	Gly		Val	Pro	Сув	Val		Thr	Gly	Asn	Gln		Arg	Сув	
			100					105					110			
TGG	GTG	GCC	CTC	ACT	CCC	ACA	GTA	GCG	TCG	CCA	TAC	GCC	GGT	GCT	CCG	384
Trp	Val		Leu	Thr	Pro	Thr		Ala	Ser	Pro	Tyr		Gly	Ala	Pro	
		115					120					125				
CTT	GAG	ccc	TTG	CGG	CGT	CAT	GTG	GAC	CTG	ATG	GTA	GGT	GCT	GCC	ACC	. 432
Leu	Glu	Pro	Leu	Arg	Arg		Val	Asp	Leu	Met	Val	Gly	Ala	Ala	Thr	
	130					135					140					
ATG	TGT	TCC	GCC	CTC	TAC	ATC	GGC	GAC	TTG	TGC	GGT	GGC	TTA	TTC	TTG	480
	Cys	Ser	Ala	Leu		Ile	Gly	Asp	Leu		Gly	Gly	Leu	Phe		
145					150					155					160	
	GGC															528
Val	Gly	Gln	Met		Thr	Phe	Gln	Pro		Arg	His	Trp	Thr	Thr	Gln	
				165					170					175		
GAC	TGC	AAT	TGT	TCC	ATC	TAC	ACG	GGC	CAC	ATT	ACG	GGT	CAT	CGG	ATG	576
Asp	Cys	Asn		Ser	Ile	Tyr	Thr		His	Ile	Thr	Gly	His	Arg	Met	
			180					185					190			
GCA																579
Ala																

## (2) INFORMATION FOR SEQ ID NO: 168:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15 WO 94/25601 PCT/EP94/01323

217

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe.
35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Thr Ser 50 55 60

Ala Val Asn Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ala Ser Ile Val Tyr Glu Thr Glu Asn His Ile Leu His
85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Gln Ser Arg Cys
100 105 110

Trp Val Ala Leu Thr Pro Thr Val Ala Ser Pro Tyr Ala Gly Ala Pro 115 120 125

Leu Glu Pro Leu Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Met Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Leu Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Thr Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 169:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 579 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..579
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 1..576

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

218

ACA Thr 1	TGC Cys	GGC Gly	TTC Phe	GCC Ala 5	GAC Asp	CTC Leu	ATG Met	GGA Gly	TAC Tyr 10	ATC Ile	CCG Pro	CTT Leu	GTA Val	GGC Gly 15	GCC Ala	48
CCC Pro	GTG Val	GGT Gly	GGC Gly 20	GTC Val	GCC Ala	AGA Arg	GCC Ala	CTG Leu 25	GCA Ala	CAC His	GGT Gly	GTT Val	AGG Arg 30	GCT Ala	GTG Val	96
	GAC Asp															144
TCT Ser	ATC Ile 50	TTC Phe	CTC Leu	TTG Leu	GCA Ala	CTT Leu 55	CTC Leu	TCG Ser	TGC Cys	CTC Leu	ACT Thr 60	GTT Val	CCC Pro	GCG Ala	TCG Ser	192
GGC Gly 65	GTT Val	AAC Asn	TAT Tyr	CGC Arg	AAT Asn 70	GCT Ala	TCG Ser	GGC	GTT Val	TAT Tyr 75	CAC His	ATC Ile	ACC Thr	AAC Asn	GAC Asp 80	240
TGC Cys	CCG Pro	AAT Asn	GCG Ala	AGC Ser 85	ATA Ile	GTG Val	TAC Tyr	GAG Glu	ACC Thr 90	GAC Asp	AAT Asn	CAC His	ATC Ile	TTA Leu 95	CAC His	288
CTC Leu	CCA Pro	GGG Gly	TGC Cys 100	GTA Val	CCC Pro	TGT Cys	GTG Val	AAG Lys 105	ACC Thr	GGG Gly	AAC Asn	CAG Gln	TCG Ser 110	CGG Arg	TGT Cys	336

TGG GTG GCC CTC ACT CCC ACA GTG GCG TCG CCT TAC GTC GGT GCT CCG 384 Trp Val Ala Leu Thr Pro Thr Val Ala Ser Pro Tyr Val Gly Ala Pro 115 120 CTC GAG CCC TTG CGG CGC CAT GTG GAC CTG ATG GTA GGT GCC ACC Leu Glu Pro Leu Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130

GTG TGC TCC GCC CTC TAC GTC GGC GAC CTG TGC GGT GGC TTA TTC TTG 480 Val Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Leu Phe Leu

GTA GGC CAA ATG TTC ACC TTC CAA CCG CGA CGC CAC TGG ACG ACC CAG Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln

GAC TGT AAT TGT TCC ATC TAC GCA GGG CAT ATT ACG GGC CAT CGG ATG 576 Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Ile Thr Gly His Arg Met 180

GCT 579 Ala

(2) INFORMATION FOR SEQ ID NO: 170:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:
- Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala
  1 5 10 15
- Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30
- Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
  35 40 45
- Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60
- Gly Val Asn Tyr Arg Asn Ala Ser Gly Val Tyr His Ile Thr Asn Asp 65 70 75 80
- Cys Pro Asn Ala Ser Ile Val Tyr Glu Thr Asp Asn His Ile Leu His 85 90 95
- Leu Pro Gly Cys Val Pro Cys Val Lys Thr Gly Asn Gln Ser Arg Cys
  100 105 110
- Trp Val Ala Leu Thr Pro Thr Val Ala Ser Pro Tyr Val Gly Ala Pro 115 120 125
- Leu Glu Pro Leu Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140
- Val Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Leu Phe Leu 145 150 155 160
- Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175
- Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 171:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 579 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA

WO 94/25601 PCT/EP94/01323 220

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..579

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 1..576

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

ACA Thr	Cys	GGC Gly	TTC Phe	GCC Ala 5	GAC Asp	CTC Leu	ATG Met	GGA Gly	TAC Tyr 10	ATC Ile	CCG Pro	CTT Leu	GTG Val	GGC Gly 15	GCC Ala	48
CCT Pro	GTT Val	GGT Gly	GGC Gly 20	GTC Val	GCC Ala	AGA Arg	GCC Ala	CTT Leu 25	GCG Ala	CAC His	GGC Gly	GTC Val	AGG Arg 30	GCT Ala	GTG Val	96
GAA Glu	GAC Asp	GGG Gly 35	ATT Ile	AAC Asn	TAT Tyr	GCA Ala	ACA Thr 40	GGG Gly	AAC Asn	CTT Leu	CCT Pro	GGT Gly 45	TGC Cys	TCC Ser	TTT Phe	144
TCT Ser	ATC Ile 50	TTC Phe	CTT Leu	CTG Leu	GCA Ala	CTT Leu 55	CTC Leu	TCG Ser	TGC Cys	CTG Leu	ACT Thr 60	GTC Val	CCC Pro	GCC Ala	TCG Ser	192
GCT Ala 65	GTG Val	CAT His	TAT	CAC His	AAC Asn 70	ACC Thr	TCG Ser	GGC Gly	ATC Ile	TAC Tyr 75	CAC His	CTC Leu	ACC Thr	AAT Asn	GAC Asp 80	240
TGC Cys	CCT Pro	AAC Asn	TCT Ser	AGC Ser 85	ATA Ile	GTC Val	TTT Phe	GAG Glu	GCA Ala 90	GTC Val	CAT His	CAC His	ATC Ile	TTG Leu 95	CAC His	288
CTT Leu	CCA Pro	GGA Gly	TGC Cys 100	GTC Val	CCT Pro	TGT Cys	GTA Val	AGA Arg 105	ACT Thr	GGG Gly	AAC Asn	CAG Gln	TCT Ser 110	CGG Arg	TGC Cys	336
TGG Trp	GTA Val	GCC Ala 115	TTG Leu	ACC Thr	CCC Pro	ACG Thr	CTG Leu 120	GCC Ala	GCG Ala	CCA Pro	TAC Tyr	CTT Leu 125	GGC Gly	GCT Ala	CCA Pro	384
CTC Leu	GAG Glu 130	TCC Ser	ATG Met	CGG Arg	CGT Arg	CAC His 135	GTG Val	GAT Asp	TTG Leu	ATG Met	GTG Val 140	GGC Gly	ACT Thr	GCT Ala	ACA Thr	432
			GCA Ala													480
			ATG Met													528

WO 94/25601 PCT/EP94/01323

221

GAG TGC AAT TGT TCC ACC TAT CCG GGC CAC ATC ACG GGT CAT AGA ATG
Glu Cys Asn Cys Ser Thr Tyr Pro Gly His Ile Thr Gly His Arg Met
180 185 190

GCG Ala

579

# (2) INFORMATION FOR SEQ ID NO: 172:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Val His Tyr His Asn Thr Ser Gly Ile Tyr His Leu Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Phe Glu Ala Val His His Ile Leu His
85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Gln Ser Arg Cys 100 105 110

Trp Val Ala Leu Thr Pro Thr Leu Ala Ala Pro Tyr Leu Gly Ala Pro 115 120 125

Leu Glu Ser Met Arg Arg His Val Asp Leu Met Val Gly Thr Ala Thr 130 135 140

Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Ile Phe Leu 145 150 155 160

Ala Gly Gln Met Phe Thr Phe Arg Pro Arg Leu His Trp Thr Thr Gln .

165 170 175

Glu Cys Asn Cys Ser Thr Tyr Pro Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

WO 94/25601 PCT/EP94/01323

(2	INFORMATION	FOR	SEO	ID	NO:	173 .

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat peptide
  - (B) LOCATION: 1..576
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:

		T TCC													
Thr C	ys Gl	y Ser	Ala	Asp	Leu	Met	Gly	Tyr	Ile	Pro	Leu	Val	Gly	Ala	
1			5					10					15		

- CCT GTG GGT GGC GTC GCC AGG GCC TTG GCG CAT GGC GTC AGG GCT GTG

  Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

  20

  25

  30
- GAG GAC GGG ATA AAC TAT GCA ACA GGG AAC CTT CCT GGT TGC TCT TTT 144
  Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
  35 40 45
- TCT ATC TTC CTT CTG GCA CTT CTC TCG TGC CTG ACT GTC CCC GCC TCA

  Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser

  50 55 60
- GCT GTG CAT TAT CAC AAC ACC TCG GGC ATC TAT CAC ATC ACT AAT GAC
  Ala Val His Tyr His Asn Thr Ser Gly Ile Tyr His Ile Thr Asn Asp
  65 70 75 80
- TGC CCT AAC TCT AGC ATA GTC TTT GAG GCA GAG CAT CAC ATC TTG CAT

  Cys Pro Asn Ser Ser Ile Val Phe Glu Ala Glu His His Ile Leu His

  85

  90

  95
- CTT CCA GGA TGC GTC CCC TGT GTG AGA ACT GGG AAC CAG TCA CGA TGC

  Leu Pro Gly Cys Val Pro Cys Val-Arg Thr Gly Asn Gln Ser Arg Cys

  100 105 110

TGG ATA GCC TTG ACC CCT ACG TTG GCC GCG CCA CAC ATT GGC GCT CCA
Trp Ile Ala Leu Thr Pro Thr Leu Ala Ala Pro His Ile Gly Ala Pro

115 120 125

CTT GAG TCC ATG CGA CGT CAT GTG GAT TTG ATG GTA GGC ACT GCC ACA
Leu Glu Ser Met Arg Arg His 135 Val Asp Leu Met Val Gly Thr Ala Thr
130 TTG TGC TCC GCA CTC TAC ATT GGA GAT CTG TGC GGA GGC ATA TTT CTA
Leu Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Ile Phe Leu
155 TTG GGC CAG ATG TTC AAC TTC AGG CCC CGC CTG CAC TGG ACC CAG
Val Gly Gln Met Phe Asn Phe Arg Pro Arg Leu His Trp Thr Thr Gln
165 TTG TAC ATC CAA GGC CAC ATC ACG GGT CAC AGA ATG

576
GAG TGC AAT TGT TCC ATC TAT CCA GGC CAC ATC ACG GGT CAC AGA ATG

GAG TGC AAT TGT TCC ATC TAT CCA GGC CAC ATC ACG GGT CAC AGA ATG
Glu Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met
180 185 190

GCG . 579

#### (2) INFORMATION FOR SEQ ID NO: 174:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

Thr Cys Gly Ser Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Val His Tyr His Asn Thr Ser Gly Ile Tyr His Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Phe Glu Ala Glu His His Ile Leu His 85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Gln Ser Arg Cys
100 -105 110

Trp Ile Ala Leu Thr Pro Thr Leu Ala Ala Pro His Ile Gly Ala Pro 115 120 125 WO 94/25601 PCT/EP94/01323

224

Leu Glu Ser Met Arg Arg His Val Asp Leu Met Val Gly Thr Ala Thr 130 135 140

Leu Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Ile Phe Leu 145 150 155 160

Val Gly Gln Met Phe Asn Phe Arg Pro Arg Leu His Trp Thr Thr Gln 165 170 175

Glu Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

#### (2) INFORMATION FOR SEQ ID NO: 175:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..576

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

ACG TGC GGC TTT GCC GAC CTC ATG GGA TAC ATC CCG CTC GTG GGC GCC

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

CCT GTG GGT GGC GTC GCC AGG GCC TTG GCA CAT GGT GTC AGG GCC GTG

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

20
25
30

GAG GAC GGG ATT AAC TAT GCA ACA GGG AAT CTT CCC GGT TGC TCC TTT

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe

35

40

45

TCT ATC TTC CTT CTA GCA CTT CTC TCG TGC TTG ACT GTC CCG GCC TCG

192

TCT ATC TTC CTT CTA GCA CTT CTC TCG TGC TTG ACT GTC CCG GCC TCG

Ser Ile Phe Leu Leu Ala Leu Leu-Ser Cys Leu Thr Val Pro Ala Ser

50

60

GCG CAG CAC TAC CGG AAC ATC TCG GGC ATT TAT CAC GTC ACC AAT GAC
Ala Gln His Tyr Arg Asn Ile Ser Gly Ile Tyr His Val Thr Asn Asp

VO 94	1/2560	01						_							PCT/EP94/	01323
								2	25							-
65					70					75					80	
TGC	CCG	AAC	TCT	AGT	ATA	GTG	TAT	GAA	GCT	GAC	CAT	CAT	ATC	ATG	CAT	288
Суз	Pro	Asn	Ser	Ser	Ile	Val	Tyr	Glu	Ala	Asp	His	His	Ile	Met	His .	200
				85			-		90	•				95		
CTA	CCA	GGG	TGT	GTG	CCT	TGC	GTG	AGA	ACC	GGG	AAC	ACC	TCG	CGC	TGC	336
Leu	Pro	Gly	Cys 100	Val	Pro	Cys	Val	Arg 105	Thr	Gly	Asn	Thr	Ser 110	Arg	Cys	
Trace	C TOM	aam	mm s													
Tro	Val	CCT	TTA	ACA	CCC	ACT	GTG	GCT	GCC	CCC	TAT	GTT	GGC	GCG	CCG	384
	val	Pro 115	Deu	1111	PIO	Int	120	Ala	ALA	PIO	Tyr	va1 125	GIÀ	Ala	Pro	
CTC	GAA	TCC	ATG	CGG	CGG	CAC	GTG	GAC	тта	ATG	GTG	CCT	acic	acc	NCC	432
Leu	Glu	Ser	Met	Arg	Arg	His	Val	Asp	Leu	Met	Val	Glv	Ala	Ala	Thr	434
	130					135					140					
GTC	TGC	TCG	GCC	CTG	TAC	ATC	GGA	GAC	CTT	TGC	GGA	GGT	GTC	TTC	CTG	480
Val	Cys	Ser	Ala	Leu		Ile	Gly	Asp	Leu	Cys	Gly	Gly	Val	Phe	Leu	
145					150					155					160	
GTC	GGG	CAG	ATG	TTC	ACC	TTC	CGG	CCG	CGC	CGC	CAT	TGG	ACT	ACC	CAG	528
Val	Gly	Gln	Met	Phe 165	Thr	Phe	Arg	Pro	Arg 170	Arg	His	Trp	Thr	Thr 175	Gln	
GAC	TGC	AAC	TGC	TCT	ATC	ТАТ	GAT	GGC	כאכ	ልጥሮ	אככ	eee	CAT	202	3.mo	
Asp	Cys	Asn	Cys	Ser	Ile	Tvr	Asp	Glv	His	Ile	Thr	Glv	Hig	ACA	Mot	576
_	-		180			-4-		185					190	ALY.	Met	
GCT																579
Ala																3.3
(2)	INFO	RMAT	ION	FOR	SEQ	ID N	io: 1	76:								
	(	i) s	EQUE	NCE	CHAR	ACTR	RIST	ics.								
	•		) LE													
			) TY													
		(D	) <b>T</b> O	POLO	GY:	line	ar									
	(ii)	MOL	ECUL	B TY	PE: j	prot	ein									

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala
1 5 10 15

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

WO 94/25601 PCT/EP94/01323

226

Ala Gln His Tyr Arg Asn Ile Ser Gly Ile Tyr His Val Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp His His Ile Met His
90
95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Thr Ser Arg Cys
100 105 110

Trp Val Pro Leu Thr Pro Thr Val Ala Pro Tyr Val Gly Ala Pro

Leu Glu Ser Met Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Val Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Arg Pro Arg Arg His Trp Thr Gln
165 170 175

Asp Cys Asn Cys Ser Ile Tyr Asp Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

#### (2) INFORMATION FOR SEQ ID NO: 177:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..576
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

ACG TGC GGG TTC GCC GAC CTC ATG GGA TAC ATC CCG CTC GTG GGC GCT

Thr Cys Gly Phe Ala Asp Leu Met-Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

CCA GTA GGA GGC GTC GCC AGA GCC TTG GCG CAT GGC GTC AGG GCT GTG 96
Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

WO 94/25601		227	PCT/EP94/01323
20	<b>)</b> .	25	30
GAG GAC GGG ATO Glu Asp Gly Ile 35	: AAT TAC GCA ACA : Asn Tyr Ala Thr 40	GGG AAC CTT CCC GGC Gly Asn Leu Pro Gly 45	TGC TCC TTT 144 Cys Ser Phe
TCT ATC TTC CTC Ser Ile Phe Lev 50	TTG GTA CTT CTC Leu Val Leu Leu 55	TCG CGC CTA ACT GTC Ser Arg Leu Thr Val	CCA GCG TCT 192 Pro Ala Ser
GCT CAG CAC TAC Ala Gln His Tyr 65	CGG AAT GCA TCG Arg Asn Ala Ser 70	GGC ATC TAC CAT GTC . Gly Ile Tyr His Val	ACC AAC GAC 240 Thr Asn Asp 80
TGC CCG AAC TCC Cys Pro Asn Ser	AGT ATT GTG TAT Ser Ile Val Tyr 85	GAA GCC GAC CAT CAC : Glu Ala Asp His His : 90	ATC ATG CAC 288 Ile Met His 95
CTA CCC GGG TGT Leu Pro Gly Cys 100	GTG CCC TGT GTA Val Pro Cys Val	AGA ACT GGG AAT GTC : Arg Thr Gly Asn Val :	TCG CGT TGC 336 Ser Arg Cys
TGG ATT CCT TTA Trp Ile Pro Leu 115	ACA CCC ACT GTA Thr Pro Thr Val 120	GCC GTC CCC TAC CTC (Ala Val Pro Tyr Leu (125	GGG GCT CCA 384 Gly Ala Pro
CTT ACG TCT GTA Leu Thr Ser Val	CGG CAG CAT GTG Arg Gln His Val 135	GAC CTG ATG GTG GGG ( Asp Leu Met Val Gly I 140	GCG GCC ACC 432 Ala Ala Thr
TTA TGC TCT GCC Leu Cys Ser Ala 145	CTC TAC ATC GGA Leu Tyr Ile Gly 150	GAC CAT TGC GGA GGT ( Asp His Cys Gly Gly 1 155	FTC TTC TTG 480 Val Phe Leu 160
GCA GGG CAG ATG Ala Gly Gln Met	GTC AGT TTC CAA Val Ser Phe Gln 165	CCC CGG CGT CAT TGG A Pro Arg Arg His Trp 7	ACT ACC CAG 528 Thr Thr Gln 175
GAT TGC AAC TGT Asp Cys Asn Cys 180	Ser Ile Tyr Val	GGC CAC ATC ACC GGC CGly His Ile Thr Gly H	CAC AGG ATG 576 His Arg Met .90
GCC Ala			579

## (2) INFORMATION FOR SEQ ID NO: 178:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

WO 94/25601 PCT/EP94/01323

228

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 10 15

Pro Val Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Phe Leu Leu Val Leu Leu Ser Arg Leu Thr Val Pro Ala Ser 50 55 60

Ala Gln His Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp
65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp His His Ile Met His 85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Thr Gly Asn Val Ser Arg Cys 100 105 110

Trp Ile Pro Leu Thr Pro Thr Val Ala Val Pro Tyr Leu Gly Ala Pro 115 120 125

Leu Thr Ser Val Arg Gln His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Leu Cys Ser Ala Leu Tyr Ile Gly Asp His Cys Gly Gly Val Phe Leu 145 150 155 160

Ala Gly Gln Met Val Ser Phe Gln Pro Arg Arg His Trp Thr Gln
165 170 175

Asp Cys Asn Cys Ser Ile Tyr Val Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

#### (2) INFORMATION FOR SEQ ID NO: 179:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:	179:
------	----------	--------------	-----	----	-----	------

ACCTGCGGCT	TCGCCGACCT	CATGGGATAC	ATCCCGCTCG	TAGGCGCCCC	CGTGGGAGGC	60
GTCGCCAGAR	CTCTGGCGCA	TGGCGTCAGG	GCTCTGGAAG	ACGGGATCAA	TTATGCAACA	120
GGGAATCTTC	CTGGTTGCTC	TTTCTCTATC	TCCCTTCTTG	AACTTCTCTC	GTGCCTGACT	180
GTTCCCGCCT	CAGCCATCCA	CTATCGCAAT	GCTTCGGACG	GTTATTATAT	CACCAATGAT	240
TGCCCGAACT	CTAGCATAGT	GTATGAAGCC	GAGAACCACA	TCTTGCACCT	TCCGGGGTGT	300
ATACCCTGTG	TGAAGACCGG	GAATCAGTCG	CGGTGCTGGG	TGGCTCTCAC	CCCCACGCTG	360
GCGGCCCCAC	ACCTACGTGC	TCCGCTTTCG	TCCTTACGGG	CGCATGTGGA	CCTAATGGTG	420
GGGCCGCCA	CGGCATGCTC	CGCTTTTTAC	ATTGGAGATC	TGTGCGGGG	TGTGTTTTTG	480
GCGGGCCAAC	TGTTCACTAT	CCGGCCACGC	ATTCATGAAA	CCACTCAGGA	CTGCAATTGC	540
TCCATCTACT	CAGGGCACAT	CACGGGTNNN	NNNNNNNN			579

#### (2) INFORMATION FOR SEQ ID NO: 180:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

#### (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Gly Val Ala Arg Xaa Leu Ala His Gly Val Arg Ala Leu 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Ser Leu Leu Glu Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Ile His Tyr Arg Asn Ala Ser Asp Gly Tyr Tyr Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Var Tyr Glu Ala Glu Asn His Ile Leu His 85 90 95

Leu Pro Gly Cys Ile Pro Cys Val Lys Thr Gly Asn Gln Ser Arg Cys
100 105 110

WO 94/25601 PCT/EP94/01323

230

Trp Val Ala Leu Thr Pro Thr Leu Ala Ala Pro His Leu Arg Ala Pro 115 Leu Ser Ser Leu Arg Ala His Val Asp Leu Met Val Gly Ala Ala Thr Ala Cys Ser Ala Phe Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 155 Ala Gly Gln Leu Phe Thr Ile Arg Pro Arg Ile His Glu Thr Thr Gln

165 170

Asp Cys Asn Cys Ser Ile Tyr Ser Gly His Ile Thr Gly Xaa Xaa Xaa 185

Xaa

### (2) INFORMATION FOR SEQ ID NO: 181:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..578

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

GCGTGCGGCT	TCGCCGATCT	CATGGGATAC	ATCCCGCTCG	TAGGCGCCCC	CGTGGGTGGC	60
GTCGCCAGAG	CCCTGGCGCA	CGGTGTTAGG	GCTGTGGAGG	ACGGGATTAA	CTACGCAACA	120
GGGAATCTTC	CTGGTTGCTC	TTTCTCTATC	TNCCTTCTGG	CACTTCTCTC	GTGCCTGACT	180
GTCCCGGCCT	CGGCTCAGCA	CTACCGGAAT	GTCTCGGGCA	TCTACCACGT	CACCAATGAT	240
TGCCCGAATT	CCAGCATAGT	GTATGAAGCC	GATCACCACA	TCATGCACTT	ACCAGGGTGC	300
ATACCCTGCG	TGAGGACCGG	GAACGTTTCG	CGCTGCTGGG	TATCTCTGAC	ACCTACTGTG .	360
GCTGCTCCCT	ACCTCGGGGC	TCCGCTTACG	TCGCTACGGC	GGCATGTGGA	TTTGATGGTG	420
GGTGCAGCCA	ררב <del>ויי</del> דייניבויר	<b>זוכררייייידי</b> ארי	GTCGGAGACC	тететеское	TOTOTOTO CONTRA	400

GTGGGACAGA TGTTCACCTT CCAGCCGCGC CGCCACTGGA CCACTCAGGA CTGCAACTGC 540
TCCATTTACG TCGGCCACAT CACAGGCCAC AGAATGGCT . 579

(2) INFORMATION FOR SEQ ID NO: 182:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 193 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

Ala Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Xaa Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Gln His Tyr Arg Asn Val Ser Gly Ile Tyr His Val Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp His His Ile Met His 85 90 95

Leu Pro Gly Cys Ile Pro Cys Val Arg Thr Gly Asn Val Ser Arg Cys
100 105 110

Trp Val Ser Leu Thr Pro Thr Val Ala Ala Pro Tyr Leu Gly Ala Pro
115 120 125

Leu Thr Ser Leu Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Val Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

WO 94/25601 PCT/EF94/01323

(2)	INF	ORMA	TION	FOR	SEC	ID	NO:	183:								
	(i	(	A) L B) T C) S	ICE C ENGT YPE: TRAN	H: 5 nuc DEDN	79 b leic ESS:	ase aci sin	pair d	s	•	f					•
	(ii	) MO	LECU	LE T	YPE:	cDN	A									
	(iii	) HY	POTH	ETIC	AL:	NO										
	(iii	) AN	TI-S	ense	: NO											
		(ix)	FEA	TURE	:											
				AME/:			579									
	/ 4				1014,		313									
	(1X	(		AME/				tide								
•		(1	B) L	OCAT	ION:	1	579									
	(xi	) SE	QUEN	CE D	ESCR	IPTI	ON:	SEQ :	ID N	0: 1:	83:					
ACC	TGC	GGC	TTT	GCC	GAC	CTC	ATG	GGA	TAC	ATC	CCG	CTC	GTA	GGC	GCC	48
Tnr 1	Сув	GIA	Phe	Ala 5	Asp	Leu	Met	Gly	Tyr 10	Ile	Pro	Leu	Val	Gly 15	Ala	
CCT	GTG	GGT	GGC	GTC	GCC	AGG	GCC	CTA	GAA	CAC	GGT	GTT	AGG	GCT	GTG	96
Pro	Val	Gly	Gly 20	Val	Ala	Arg	Ala	Leu 25	Glu	His	Gly	Val	Arg	Ala	Val	
GAG	GAC	GGT	ATT	AAT	тат	GCA	ACA	GGG	ልልጥ	CTP.C	ccc			ملحك	unterte	144
Glu	Asp	Gly 35	Ile	Asn	Tyr	Ala	Thr	Gly	Asn	Leu	Pro	Gly	Сув	Ser	Phe	744
TO T	3.000		~~~									45				
Ser	ATC Ile	Ser	Leu	Leu	Ala	Leu	Leu	Ser	TGC Cys	CTG Leu	ACT Thr	GTT Val	CCC Pro	ACC Thr	TCA Ser	192
	50					55					60					
GCC Ala	GTC Val	AAC Asn	TAT Tyr	CGC Arg	AAC Asn	GCC Ala	TCG Ser	GGC Gly	GTC Val	TAT	CAT His	ATC Ile	ACC Thr	AAT Asn	GAC	240
65			_	•	70					75					80	
TGC	CCG	AAT	TCG	AGC	ATA	GTG	TAC	GAG	GCT	GAC	TAC	CAC	ATC	CTA	CAC	288
-ys	Pro	waii	SEL	85	115	val	TÄE	GIU	90	Asp	TYT	HIS	TTE	Leu 95	HIS	

CTC CCT GGG TGC TTA CCC TGC GTG AGG GTT GGG AAT CAG TCA CGC TGC

Leu Pro Gly Cys Leu Pro Cys Val Arg Val Gly Asn Gln Ser Arg Cys

TGG GTG GCC CTT ACT CCC ACC GTG GCG GCG CCT TAC GTT GGT GCT CCG

Trp Val Ala Leu Thr Pro Thr Val Ala Ala Pro Tyr Val Gly Ala Pro

336

<b>VO</b> 5	4/256	01				•		•	233				٠		PCT/	EP94/01323	
		115	<b>5</b>				120					125					
		Ser				CAT His 135						Gly			ACT Thr	432	2
GTG Val 145	Cys	TCC Ser	GCT Ala	CTT	TAC Tyr 150	ATC Ile	GGG Gly	GAC Asp	CTG Leu	TGC Cys 155	GGT Gly	GGC Gly	GTA Val	TTT	TTG Leu 160	480	)
GTT Val	GGT	CAG Gln	ATG Met	TTT Phe 165	Ser	TTC Phe	CAG Gln	CCG Pro	CGA Arg 170	CGC Arg	CAC His	TGG Trp	ACC Thr	ACG Thr 175	CAG Gln	528	ļ
GAC Asp	TGC Cys	AAT Asn	TGT Cys 180	TCT Ser	ATC	TAC Tyr	GCG Ala	GGG Gly 185	CAC	GTT Val	ACG Thr	GGC Gly	CAC His 190	AGG	ATG Met	576	;
GCA Ala																579	,
(2)	INF	ORMA	TION	FOR	SEQ	ID 1	NO: 3	184:									
		(, ()	A) Li B) T	engti Ype :	H: 19 ami:	RACTI 93 am no ac line	nino										
	(ii) MOLECULE TYPE: protein																
					IPE:	proc	.ein										
	(xi	SE(				PTIC		SEQ :	ID NO	): 18	34:						
Thr 1			QUEN	CE DI	SSCR:	_	ON: S					Leu	Val	Gly 15	Ala		
1	Сув	Gly	QUENC Phe	CE DI Ala 5	SCR:	- IPTIC	ON: S	Gly	Tyr 10	Ile	Pro			15			
1 Pro	Cys Val	Gly	Phe Gly 20	CE DI Ala 5 Val	Asp Ala	IPTIC	ON: S Met Ala	Gly Leu 25	Tyr 10 Ala	Ile His	Pro Gly	Val	Arg 30	15 Ala	Val		
1 Pro Glu	Cys Val Asp	Gly Gly Gly 35	Phe Gly 20	Ala 5 Val Asn	Asp Ala Tyr	Leu Arg	Met Ala Thr	Gly Leu 25 Gly	Tyr 10 Ala Asn	Ile His Leu	Pro Gly Pro	Val Gly 45	Arg 30 Cys	15 Ala Ser	Val Phe		
1 Pro Glu Ser	Cys Val Asp Ile 50	Gly Gly 35 Phe	Phe Gly 20 Ile	Ala 5 Val Asn Leu	Asp Ala Tyr Ala	Leu Arg Ala Leu	Met Ala Thr 40 Leu	Gly Leu 25 Gly Ser	Tyr 10 Ala Asn Cys	Ile His Leu Leu	Pro Gly Pro Thr 60	Val Gly 45 Val	Arg 30 Cys Pro	15 Ala Ser Thr	Val Phe Ser		
Pro Glu Ser Ala 65	Val Asp Ile 50	Gly Gly 35 Phe	Phe Gly 20 Ile Leu Tyr	Ala 5 Val Asn Leu	Asp Ala Tyr Ala Asn 70	Leu Arg Ala Leu 55	Met Ala Thr 40 Leu Ser	Gly Leu 25 Gly Ser	Tyr 10 Ala Asn Cys	Ile His Leu Leu Tyr 75	Pro Gly Pro Thr 60	Val Gly 45 Val	Arg 30 Cys Pro	15 Ala Ser Thr	Val Phe Ser Asp		
1 Pro Glu Ser Ala 65 Cys	Val Asp Ile 50 Val	Gly Gly 35 Phe Asn	Phe Gly 20 Ile Leu Tyr	Ala 5 Val Asn Leu Arg	Asp Ala Tyr Ala Asn 70 Ile	Leu Arg Ala Leu 55	Met Ala Thr 40 Leu Ser Tyr	Gly Leu 25 Gly Ser Gly	Tyr 10 Ala Asn Cys Ile Thr 90	Ile His Leu Tyr 75 Glu	Pro Gly Pro Thr 60 His	Val Gly 45 Val Ile His	Arg 30 Cys Pro Thr	15 Ala Ser Thr Asn Leu 95	Val Phe Ser Asp 80		
1 Pro Glu Ser Ala 65 Cys	Val Asp Ile 50 Val Pro	Gly Gly 35 Phe Asn Gly	QUENC Phe Gly 20 Ile Leu Tyr Ala Cys 100	Ala 5 Val Asn Leu Arg Ser 85	Asp Ala Tyr Ala Asn 70 Ile	Leu Arg Ala Leu 55 Ala Val Cys	Met Ala Thr 40 Leu Ser Tyr	Gly Leu 25 Gly Ser Gly Glu Arg 105	Tyr 10 Ala Asn Cys Ile Thr 90	Ile His Leu Tyr 75 Glu Gly	Pro Gly Pro Thr 60 His Asn	Val Gly 45 Val Ile His	Arg 30 Cys Pro Thr Ile Ser 110	15 Ala Ser Thr Asn Leu 95	Val Phe Ser Asp 80 His		

Met Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Leu Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Thr Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 182:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 192 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

Ala Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 40 45

Ser Ile Ser Phe Trp His Phe Ser Arg Ala \* Leu Ser Arg Pro Arg 50 55 60

Leu Ser Thr Thr Gly Met Ser Arg Ala Ser Thr Thr Ser Pro Met Ile
65 70 75 80

Ala Arg Ile Pro Ala \* Cys Met Lys Pro Ile Thr Thr Ser Cys Thr 85 90 95

Tyr Gln Gly Ala Tyr Pro Ala \* Gly Pro Gly Thr Phe Arg Ala Ala 100 105 110

Gly Tyr Leu \* His Leu Leu Trp Leu Leu Pro Thr Ser Gly Leu Arg 115 120 125

Leu Arg Arg Tyr Gly Gly Met Trp Ile \* Trp Trp Val Gln Pro Pro 130 135 140

Phe Ala Leu Pro Ser Thr Ser Glu Thr Ser Val Glu Val Ser Ser \*
145 150 155 160

Trp Asp Arg Cys Ser Pro Ser Ser Arg Ala Ala Thr Gly Pro Leu Arg 165 170 175

Thr Ala Thr Ala Pro Phe Thr Ser Ala Thr Ser Gln Ala Thr Glu Trp

WO 94/25601

PCT/EP94/01323

180 185 . 190

235

#### (2) INFORMATION FOR SEQ ID NO: 185:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..576

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

			GAC Asp						48
			GCC Ala						96
			TAT Tyr						144
			GCA Ala						192
GCC Ala 65			AAT Asn 70						240
TGC Cys									288
CTT									336

TGG GTG GCC CTC TCT CCC ACC GTG GCG GCG CCT TAC ATC GGT GCT CCA

WO 94	1/2560	)1						2	236						PCT/I	<b>EP94/0</b> :	1323
Trp	Val	. Ala		Ser	Pro	Thr	Val 120		Ala	Pro	Tyr	Ile 125		Ala	Pro		
		Ser					Val					Gly			ACT Thr	•	432
GTG Val 145	Cys	TCC Ser	GCT	CTC Leu	TAT Tyr 150	ATT	GGG	GAC Asp	TTG Leu	TGT Cys 155	GGT Gly	GGC Gly	GTA Val	TTC Phe	TTG Leu 160		480
GTT Val	GGT Gly	CAG Gln	ATG Met	TTT Phe 165	TCT Ser	TTC Phe	CGG Arg	CCA Pro	CGA Arg 170	CGC Arg	CAC His	TGG Trp	ACT Thr	ACG Thr 175	CAG Gln		528
GAC Asp	TGC Cys	AAT Asn	TGT Cys 180	TCC Ser	ATC Ile	TAC Tyr	GCG Ala	GGG Gly 185	CAC His	ATC Ile	ACT Thr	GGC Gly	CAC His 190	GGA Gly	ATG Met		576
GCA Ala																	579
(2)	(ii)	(i)	FION SEQUIA) LI B) TO D) TO LECUI	ence engti (PE: OPOLA	CHAI H: 19 amin DGY:	RACTI 93 am no ac line prot	ERIST mino cid ear	FICS:	ls	): 18	<b>36</b> :						
Thr 1	Сув	Gly	Phe	Ala 5	Asp	Leu	Met	Gly	Tyr 10	Ile	Pro	Leu	Val	Gly 15			
Pro	Val	Gly	Gly 20	Val	Ala	Arg	Ala	Leu 25	Glu	His	Glÿ	Val	Arg 30	Ala	Val		
Glu	Asp	Gly 35	Ile	Asn	Tyr	Ala	Thr 40	Gly	Asn	Leu	Pro	Gly 45	Cys	Ser	Phe		
Ser	Ile 50	Tyr	Leu	Leu	Ala	Leu 55	Leu	Ser	Сув	Leu	Thr 60	Val	Pro	Thr	Ser		
Ala 65	Ile	His	Tyr	Arg	Asn 70	Ala	Ser	Gly	Val	Tyr 75		Val	Thr	Asn	qaA 08		
Cys	Pro	Asn	Ser	Ser 85	Ile	Val	Tyr	Glu	Ala 90	Asp	His	His	Ile	Leu 95	His		
Leu	Pro	Gly	Cys 100	Leu	Pro	Сув		Arg 105	Val	Gly	Asn	Gln	Ser 110	Arg	Суз		
Trp	Val	Ala	Leu	Ser	Pro	Thr	Val	Ala	Ala	Pro	Tyr	Ile	Gly	Ala	Pro		

WO 94/25601 PCT/EP94/01323 237 Val Glu Ser Phe Arg Arg His Val Asp Met Met Val Gly Ala Ala Thr Val Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 155 Val Gly Gln Met Phe Ser Phe Arg Pro Arg Arg His Trp Thr Thr Gln Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Ile Thr Gly His Gly Met 185 Ala (2) INFORMATION FOR SEQ ID NO: 187: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 579 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1..579 (ix) FEATURE: (A) NAME/KEY: mat\_peptide (B) LOCATION: 1..576 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187: ACT TGC GGC TTT GCC GAC CTC ATG GGA TAC ATC CCG CTC GTA GGC GCC 48 Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

# GCC GTC AAC TAT CGC AAT GCC TCG GGC ATC TAT CAC ATC ACC AAT GAC

CCT GTG GGT GGC GTC GCC AGG GCC CTG GCA CAC GGT GTT AGG GCT GTG

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val

GAG GAC GGG ATC AAT TAT GCG ACA GGG AAT CTT CCC GGT TGC TCT TTC

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe

TCT ATC TTC CTC TTG GCA CTT CTT-TCG TGC CTG ACT GTT CCC ACC TCG

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Thr Ser

20

35

50

96

144

192

WO 9	4/2560	1				•		2	38						PCT/EP94/0	1323
Ala 65	Val	Asn	Tyr	Arg	Asn 70	Ala	Ser	Gly	Ile	Tyr 75	His	Ile	Thr	Asn	Asp 80	
	CCG															288
Cys	Pro	Asn	Ser	Ser	Ile	Val	Tyr	Glu	Thr	Glu	His	His	Ile	Leu	His	
				85			<b>-</b> :		90					95		
	CCA															336
Leu	Pro	GIY	Cys 100	Leu	Pro	Сув	Val	Arg 105	Val	Gly	Asn	Gln	Ser 110	Arg	Cys	
TGG	GTG	GCC	CTC	ACT	CCC	ACC	GTG	GCG	GCG	CCT	TAC	ATC	GGC	GCT	CCG	384
Trp	Val	Ala	Leu	Thr	Pro	Thr	Val	Ala	Ala	Pro	Tyr	Ile	Gly	Ala	Pro	55.
		115					120					125				
	GAA															432
Leu	Glu	Ser	Leu	Arg	Ser		Val	qaA	Leu	Met		Gly	Ala	Ala	Thr	
	130					135					140					
	TGC															480
145	Cys	ser	Ala	Leu	Tyr 150	Ile	Gly	Asp	Leu		Gly	Gly	Val	Phe		
								٠		155					160	
GŢŢ	GGT	CAG	ATG	TTC	TCT	TTC	CAG	CCG	CGG	CGC	CAC	TGG	ACT	ACG	CAG	528
Val	Gly	Gln	Met		Ser	Phe	Gln	Pro		Arg	His	Trp	Thr		Gln	
				165					170					175		
	TGC															576
qaA	Cys	Asn	Cys 180	Ser	Ile	Tyr	Ala	Gly 185	His	Val	Thr	Gly		Arg	Met	
			100					105					190		•	
GCA																579
Ala																
(2)	INFO	RMAT	NOI	FOR	SEQ	ID N	io: 1	.88:								
	(			NCE NGTH							•					
				PE:				acic	15							
				POLO												
	(ii)	MOL	ECUL	E TY	PE:	prot	ein									
	(xi)	SEQ	UENC	E DE	SCRI	PTIO	N: S	EQ I	D NO	): 18	8:					
Thr	Сув	Gly	Phe	Ala	Asp	Leu	Met	Gly	Tyr	Ile	Pro	Leu	Val	Gly	Ala	
1				5					10					15		
Pro	Val	Gly	Gly	Val	Ala	Arg	Ala	Leu	Ala	His	Gly	Val	Arg	Ala	Val	
			20			-		25			-		30			
Glu	Asp	Gly	Ile .	Asn	Tyr	Ala	Thr -	Gly	Asn	Leu	Pro	Gly	Cys	Ser	Phe	
		35					40	-				45	-	•		

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Thr Ser

. 55

Ala Val Asn Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp
65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Thr Glu His His Ile Leu His 85 90 95

Leu Pro Gly Cys Leu Pro Cys Val Arg Val Gly Asn Gln Ser Arg Cys
100 105 110

Trp Val Ala Leu Thr Pro Thr Val Ala Ala Pro Tyr Ile Gly Ala Pro 115 120 125

Leu Glu Ser Leu Arg Ser His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Ala Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Ser Phe Gln Pro Arg Arg His Trp Thr Thr Gln
165 170 175

Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Val Thr Gly His Arg Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 189:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 579 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..579
  - (ix) FEATURE:
    - (A) NAME/KEY: mat peptide
    - (B) LOCATION: 1..576
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

ACG TGC GGC TTC GCC GAC CTC ATG GGA TAC ATC CCG CTC GTG GGC GCC
Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala

1 5 10 15

48

ľ

WO 94	1/2560	1				•		_							PCT/	EP94/01323
								2	40	_						
CCC Pro	GTT Val	GGG	GGC Gly 20	GTC Val	GCC Ala	AGG Arg	GCC Ala	CTG Leu 25	GCG Ala	CAT	GGC Gly	GTC Val	AGG Arg 30	GCT Ala	GTG Val	96
					TAT Tyr										TTC Phe	144
					GCA Ala										TCA Ser	192
					AAT Asn 70											240
					GTA Val											288
					CCC Pro											336
					CCT Pro											384
CTC Leu	GAG Glu 130	TCC Ser	TTC Phe	CGG Arg	CGG Arg	CAT His 135	GTG Val	GAC Asp	CTA Leu	ATG Met	GTA Val 140	GGT Gly	GCG Ala	GCC Ala	ACC Thr	432
					TAT Tyr 150											480
GTG Val	GGG Gly	CAG Gln	ATG Met	TTC Phe 165	ACC Thr	TTC Phe	CAG Gln	CCG Pro	CGT Arg 170	CGC Arg	CAC His	TGG Trp	ACC Thr	ACG Thr 175	CAG Gln	528
GAT Asp	TGT Cys	AAT Asn	TGC Cys 180	TCC Ser	ATC Ile	TAT Tyr	ACT Thr	GGC Gly 185	CAT His	ATC Ile	ACC Thr	Gly	CAC His 190	AGG Arg	ATG Met	576
GCG Ala																579

# (2) INFORMATION FOR SEQ ID NO: 190:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val 20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe
35 40 45

Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 55 60

Ala Glu His Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile Thr Asn Asp 65 70 75 80

Cys Pro Asn Ser Ser Val Val Tyr Glu Thr Asp His His Ile Leu His 85 90 95

Leu Pro Gly Cys Val Pro Cys Val Arg Ala Gly Asn Val Ser Arg Cys
100 105 110

Trp Thr Pro Val Thr Pro Thr Val Ala Ala Val Ser Met Asp Ala Pro
115 120 125

Leu Glu Ser Phe Arg Arg His Val Asp Leu Met Val Gly Ala Ala Thr 130 135 140

Val Cys Ser Val Leu Tyr Val Gly Asp Leu Cys Gly Gly Ala Phe Leu 145 150 155 160

Val Gly Gln Met Phe Thr Phe Gln Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Thr Gly His Ile Thr Gly His Arg Met 180 185 190

Ala

## (2) INFORMATION FOR SEQ ID NO: 191:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 289 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS

WO 94/25601

PCT/EP94/01323

242

(B) LOCATION: 1..289

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 1..286

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

ATG AGC ACG AAT CCT AAA CCT CAA AGA AAA ACC AAA CGT AAC ACC AAC 48 Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn CGC CGC CCC ATG GAC GTT AAG TTC CCG GGC GGT GGC CAG ATC GTT GGT 96 Arg Arg Pro Met Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly GGA GTT TAC TTG TTG CCG CGC AGG GGC CCC AGG TTG GGT GTG CGC GCG Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala 35 ACT AGG AAG ACT TCG GAG CGG TCG CAA CCT CGT GGG AGA CGT CAG CCT Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro . 50 ATC CCC AAG GCA CGT CGA TCT GAG GGA AGG TCC TGG GCT CAG CCC GGG 240 Ile Pro Lys Ala Arg Arg Ser Glu Gly Arg Ser Trp Ala Gln Pro Gly TAC CCA TGG CCT CTT TAC GGT AAT GAG GGT TGT GGG TGG GCA GGA TGG G Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp

- (2) INFORMATION FOR SEQ ID NO: 192:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 96 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn 1 5 10 15

Arg Arg Pro Met Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly
20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
50 55 60

Ile Pro Lys Ala Arg Arg Ser Glu Gly Arg Ser Trp Ala Gln Pro Gly

	·	
WO 94/25601	243	PCT/EP94/01323
65 . 70		80
Tyr Pro Trp Pro Leu Tyr	r Gly Asn Glu Gly Cys Gly	
85	90	95 ·
(2) INFORMATION FOR SEC	Q ID NO: 193:	
(i) SEQUENCE CHARF (A) LENGTH: 4 (B) TYPE: NUC (C) STRANDEDN (D) TOPOLOGY:	98 base pairs :leic acid ESS: single	
(ii) MOLECULE TYPE:	cDNA	
(iii) HYPOTHETICAL:	NO	
(iii) ANTI-SENSE: NO		
(ix) FEATURE: (A) NAME/KEY:	CDS	
(B) LOCATION:	1498	
(ix) FEATURE: (A) NAME/KEY:	mat_peptide	
(B) LOCATION:	1495	
(xi) SEQUENCE DESCR	IPTION: SEQ ID NO: 193:	
ATG AGC ACG AAT CCT AAA	CCT CAA AGA AAA ACC AAA	CGT AAC ACC AAC 48
Met Ser Thr Asn Pro Lys 1 5	Pro Gln Arg Lys Thr Lys 10	Arg Asn Thr Asn 15
CGC CGC CCT ATG GAC GTA	AAG TTC CCG GGC GGT GGA	CAG ATC GTT GGC 96
Arg Arg Pro Met Asp Val 20	Lys Phe Pro Gly Gly Gly 25	Gln Ile Val Gly 30
GGA GTT TAC TTG TTG CCG	CGC AGG GGC CCC CGG TTG	GGT GTG CGC GCG 144
Gly Val Tyr Leu Leu Pro 35	Arg Arg Gly Pro Arg Leu 40	Gly Val Arg Ala 45
ACT CGG AAG ACT TCG GAG	CGG TCG CAA CCT CGT GGC	AGG CGT CAA CCT 192
Thr Arg Lys Thr Ser Glu 50	Arg Ser Gln Pro Arg Gly 55 60	Arg Arg Gln Pro
ATC CCC AAG GCG CGC CGG Ile Pro Lys Ala Arg Arg		

Ile Pro Lys Ala Arg Arg Ser Glu Gly Arg Ser Trp Ala Gln Ala Gly

TAC CCC TGG CCC CTC TAT GGC AAT GAG GGC TGT GGG TGG GCA GGG TGG

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp

CTC CTG TCT CGC GGC TCT CGG CCA TCT TGG GGC CCA AAT GAT CCC

288

336

wo 9	4/256	01							244						PCT/E	P94/01323	
Let	ı Let	Sez	100		Gly	Ser	Arg	Pro		Trp	Gly	Pro	Asn 110	_	Pro		
CG(	G CGG	AGA Arg	, Ser	CGC	AAT Asn	CTG Leu	GGT Gly 120	Lys	GTC Val	Ile	GAT Asp	ACC Thr 125	CTG Leu	ACG	TGC Cys	· 384	1
GGC Gly	Phe	Ala	GAC Asp	CTC Leu	ATG Met	GGA Gly 135	TAC Tyr	ATC	CCG Pro	CTC Leu	GTG Val 140	GGC Gly	GCC Ala	CCC	GTC Val	432	1
GGG Gly 145	Gly	GTC Val	GCC Ala	AGG Arg	GCC Ala 150	CTG Leu	GCG Ala	CAT	GGC	GTC Val 155	AGG Arg	GCT Ala	GTG Val	GAG Glu	GAC Asp 160	480	ł
			TAT													498	
(2)	INF	ORMA	TION	FOR	SEQ	ID 1	10: :	L94:									
		()	SEQU A) Li B) T D) T	engti Ype :	H: 10 ami	se an	nino cid										
	(ii	) MO	T ECTY														
						prot		ero :	rto No		34.						
Met 1	(xi	) SE	QUEN( Asn	CE DI	SCR:	IPTIC	N: S					Arg	Asn	Thr 15	Asn		
1	(xi	SE Thr	QUEN	CE DI Pro 5	ESCR:	Pro	N: S	Arg	Lys 10	Thr	Lys			15			
1 Arg	(xi Ser Arg	SE Thr Pro	QUENC Asn Met 20 Leu	Pro 5 Asp	ESCR: Lys Val	Pro Lys	ON: S Gln Phe	Arg Pro 25	Lys 10 Gly	Thr Gly	Lys · Gly	Gln	Ile 30	15 Val	Gly		
Arg Gly	(xi Ser Arg Val	Thr Pro Tyr 35	QUENC Asn Met 20 Leu	Pro 5 Asp	Lys Val Pro	Pro Lys	ON: S Gln Phe Arg 40	Arg Pro 25 Gly	Lys 10 Gly Pro	Thr Gly Arg	Lys Gly Leu	Gln Gly 45	Ile 30 Val	15 Val Arg	Gly Ala		
Arg Gly Thr	(xi) Ser Arg Val Arg 50	Thr Pro Tyr 35	QUENC Asn Met 20 Leu	Pro 5 Asp Leu Ser	Lys Val Pro	Pro Lys Arg Arg	ON: S Gln Phe Arg 40 Ser	Arg Pro 25 Gly Gln	Lys 10 Gly Pro	Thr Gly Arg Arg	Lys Gly Leu Gly 60	Gln Gly 45 Arg	Ile 30 Val Arg	15 Val Arg Gln	Gly Ala Pro		
Arg Gly Thr	(xi Ser Arg Val Arg 50	Thr Pro Tyr 35 Lys	QUENC Asn Met 20 Leu	Pro 5 Asp Leu Ser	Lys Val Pro Glu Arg 70	Pro Lys Arg Arg 55	ON: SGIn  Phe  Arg 40  Ser	Pro 25 Gly Gln	Lys 10 Gly Pro Pro	Thr Gly Arg Arg Ser 75	Lys Gly Leu Gly 60	Gln Gly 45 Arg Ala	Ile 30 Val Arg Gln	Val Arg Gln Ala	Gly Ala Pro Gly 80		
Arg Gly Thr Ile 65	(xi Ser Arg Val Arg 50 Pro	Thr Pro Tyr 35 Lys Lys	QUENC Asn Met 20 Leu Thr	Pro 5 Asp Leu Ser Arg	Lys Val Pro Glu Arg 70	Pro Lys Arg Ser Gly	ON: SGIn Phe Arg 40 Ser Glu Asn	Arg Pro 25 Gly Gln Gly	Lys 10 Gly Pro Pro Arg Gly 90	Thr Gly Arg Arg Cys	Lys Gly Leu Gly 60 Trp	Gln Gly 45 Arg Ala	Ile 30 Val Arg Gln Ala	Val Arg Gln Ala Gly 95	Gly Ala Pro Gly 80 Trp		
Arg Gly Thr Ile 65 Tyr	(xi Ser Arg Val Arg 50 Pro	Thr Pro Tyr 35 Lys Trp Ser	QUENC Asn Met 20 Leu Thr Ala Pro	Pro 5 Asp Leu Ser Arg Leu 85	Lys Val Pro Glu Arg 70 Tyr	Pro Lys Arg Arg Ser Gly Ser	ON: SGIn Phe Arg 40 Ser Glu Asn	Arg Pro 25 Gly Gln Gly Glu Pro 105	Lys 10 Gly Pro Pro Arg Gly 90 Ser	Thr Gly Arg Arg Cys	Lys Gly Gly Gly Gly Asp	Gln Gly 45 Arg Ala Trp	Ile 30 Val Arg Gln Ala Asn	Val Arg Gln Ala Gly 95 Asp	Gly Ala Pro Gly 80 Trp		

WO 94/25601 PCT/EP94/01323 245 Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Ala Val Glu Asp 150 155 Gly Ile Asn Tyr Arg Gln (2) INFORMATION FOR SEQ ID NO: 195: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 579 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iii) ANTI-SENSE: NO (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1..579 (ix) FEATURE: (A) NAME/KEY: mat\_peptide (B) LOCATION: 1..576 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195: ACG TGC GGA TTC GCC GAC CTC GTG GGG TAC ATC CCG CTC GTA GGC GGC 48 Thr Cys Gly Phe Ala Asp Leu Val Gly Tyr Ile Pro Leu Val Gly Gly 1 5 15 CCC GTT GGG GGC GTC GCA AGG GCT CTC GCA CAT GGT GTG AGG GTT CTT 96 Pro Val Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu 20 GAG GAC GGG GTG AAT TAT GCA ACA GGG AAT CTG CCT GGT TGC TCT TTC 144 Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35 TCT ATC TTC ATT CTT GCA CTT CTC TCG TGC CTC ACT GTC CCG GCC TCT 192 Ser Ile Phe Ile Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser 50 GCA GTT CCC TAC CGA AAT GCC TCT GGG ATC TAT CAT GTC ACC AAT GAT 240 Ala Val Pro Tyr Arg Asn Ala Ser Gly Ile Tyr His Val Thr Asn Asp 65 75

TGC CCA AAC TCT TCC ATA GTC TAT GAG GCA GAT GAT CTG ATC CTA CAC

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp Asp Leu Ile Leu His

GCA CCT GGC TGC GTG CCT TGT GTC AGG AAA GAT AAT GTG AGT AGG TGC

85

288

VO 9	4/256	01				•		2	46						PCT/I	EP94/01323	3
Ala	Pro	Gly	Cys		Pro	Cys	Val	Arg	Lys	Asp	Asn	Val	Ser 110	_	Cys		
			Ile					Ser	GCC Ala						GTC Val	· 38	4
		Pro							TAC							43	2
	Суз								GCG Ala							48	0
GTA Val	GGC	CAA Gln	ATG Met	TTC Phe 165	ACC Thr	TAT Tyr	AGG Arg	CCT Pro	CGC Arg 170	CAG Gln	CAT His	GCT Ala	ACG Thr	GTG Val	CAG Gln	52	8
GAC Asp	TGC Cys	AAC Asn	TGT Cys 180	TCC Ser	ATC Ile	TAC Tyr	AGT Ser	GGC Gly 185	CAC His	GTC Val	ACC Thr	GGC Gly	CAT His 190	CAG	ATG Met	57	6
GCA Ala												•				57	9
(2)		(1) (3)	SEQUI A) LI B) T	ence Engti Ype :	SEQ CHAI H: 1! amin	RACTI 93 at	KRIS: mino cid	rics									
	( <b>i</b> i)				YPE:						•						
	(xi	SE	QUENC	CE DI	ESCR:	[PTI	ON: 8	SEQ :	ID NO	): 19	96 :						
Thr 1	Сув	Gly		Ala 5		Leu	Val	Gly	Tyr 10	Ile	Pro	Leu	Ϋal	Gly 15	Gly		
Pro	Val	Gly	Gly 20	Val	Ala	Arg	Ala	Leu 25	Ala	His	Gly	Val	Arg 30	Val	Leu		
3lu	Asp	Gly 35	Val	Asn	Tyr	Ala	Thr 40	Gly	Asn	Leu	Pro	Gly 45	Cys	Ser	Phe		
Ser	Ile 50	Phe	Ile	Leu	Ala	Leu 55	Leu	Ser	Сув	Leu	Thr 60	Val	Pro	Ala	Ser		
Ala 65	Val	Pro	Tyr	Arg	Asn 70	Ala	Ser	Gly	Ile	Tyr 75	His	Val	Thr	Asn	Asp 80		
<b>:</b> ys	Pro	Asn	Ser	Ser 85	Ile	Val	Tyr	Glu	Ala 90	Asp	Asp	Leu	Ile	Leu 95	His		
lla	Pro	Gly	Cys	Val	Pro	Cys	Val	Arg	Lys	Asp	Asn	Val	Ser	Arg	Сув		

WO 94/25601 PCT/EP94/01323 247

Trp Val Gln Ile Thr Pro Thr Leu Ser Ala Pro Ser Phe Gly Ala Val 120

Thr Ala Pro Leu Arg Arg Ala Val Asp Tyr Leu Val Gly Gly Ala Ala

Leu Cys Ser Ala Leu Tyr Val Gly Asp Ala Cys Gly Ala Leu Phe Leu

Val Gly Gln Met Phe Thr Tyr Arg Pro Arg Gln His Ala Thr Val Gln 170

Asp Cys Asn Cys Ser Ile Tyr Ser Gly His Val Thr Gly His Gln Met 185

Ala

## (2) INFORMATION FOR SEQ ID NO: 197:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 579 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 1..579
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 1..576

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

ACT TGC GGC TTT GCC GAC CTC ATG GGA TAC ATC CCG CTC GTA GGC GCC Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala 1

CCC GTG GGT GGC GTC GCC AGA GCC CTG GAA CAT GGT GTT AGG GCT GTG 96 Pro Val Gly Gly Val Ala Arg Ala Leu Glu His Gly Val Arg Ala Val 20

GAG GAC GGC ATC AAT TAT GCA ACA-GGG AAT CTC CCC GGT TGC TCT TTC Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe 35

TCT ATC TAC CTC TTG GCA CTT CTC TCG TGC CTG ACT GTT CCC ACC TCG 192

# (2) INFORMATION FOR SEQ ID NO: 198:

Ala

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 193 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala
1 5 10 15

Pro Val Gly Val Ala Arg Ala Leu Glu His Gly Val Arg Ala Val
20 25 30

Glu Asp Gly Ile Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe

40

45

Ser Ile Tyr Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Thr Ser 50 55 60

Ala Ile His Tyr Arg Asn Ala Ser Gly Val Tyr His Val Thr Asn Asp
65 70 75 80

Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Asp His His Ile Leu His
85 90 95

Leu Pro Gly Cys Leu Pro Cys Val Arg Val Gly Asn Gln Ser Arg Cys
100 105 110

Trp Val Ala Leu Ser Pro Thr Val Ala Ala Pro Tyr Ile Gly Ala Pro
115 120 125

Val Glu Ser Phe Arg Arg His Val Asp Met Met Val Gly Ala Ala Thr 130 135 140

Val Cys Ser Ala Leu Tyr Ile Gly Asp Leu Cys Gly Gly Val Phe Leu 145 150 155 160

Val Gly Gln Met Phe Ser Phe Arg Pro Arg Arg His Trp Thr Thr Gln 165 170 175

Asp Cys Asn Cys Ser Ile Tyr Ala Gly His Ile Thr Gly His Gly Met 180 185 190

Ala

- (2) INFORMATION FOR SEQ ID NO: 199:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 1470 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..1470
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
      - (B) LOCATION: 2..1467
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

WO 94	4/2560	<b>D1</b>				•		2	2 <b>50</b>						PCT/	EP94/01323
A :	CA ( Ser 1	CCA (	ccg o	BAG (	TT C eu I 5	TA T Leu S	CA C	CAT # Lis T	ACT C	CA C Pro I	TT : eu 1	CG G	CA A	GT T	CC Ser 15	46
TT( Let	G CTO	ATO	GAC	GGT Gly 20	' Val	CAG Gln	GCG Ala	GCG Ala	CGC Arg	Met	ACG Thr	TGA			GCG Ala	94
ACC Thr	G AGI	GCC Ala	ATI Ile 35	Pro	AGG Arg	ACG Thr	CCA Pro	CCA Pro 40	Pro	TTC Phe	TTG Leu	GGA Gly	TAG * *	Ala	CTG Leu	142
TCC Ser	Leu	ACC Thr	Arg	CAG Gln	AGA Arg	CGG Arg	CTG Leu 55	Glu	CTA Leu	GGC Gly	TCG Ser	TCG Ser 60	Ser	TGG Trp	CCA Pro	190
CGG Arg	Pro 65	Pro	CTC Leu	CCG Pro	GCA Ala	GTG Val 70	TGA	CAA Gln	CGC Arg	Pro	ACC Thr 75	Pro	ACA Thr	TCG Ser	AGG Arg	238
AAG Lys 80	Trp	Pro	TGC Cys	CTC	AGG Arg 85	AGG Arg	GGG Gly	AGG Arg	TTC Phe	CCT Pro 90	TCT	ACG Thr	GCA Ala	GAG Glu	CCA Pro 95	<b>286</b>
Phe	Pro	Leu	Leu	Leu 100	*	Arg	Val	Val	Gly 105	Ile	Ser	Ser	Ser	Ala 110	ATT Ile	334
CCA Pro	AGA Arg	AAA Lys	AAT Asn 115	GTG Val	ATG Met	AAC Asn	TCG Ser	CCA Pro 120	AGC Ser	AAC Asn	TGA *	CCA Pro	GCC Ala 125	TGG Trp	GCG Ala	382
*	Thr	Pro 130	TGG Trp	His	Ile	Ile	Glu 135	Val	*	Thr	Ser	Pro 140	Ser	Tyr	Pro	430
Gln	Gln 145	Glu	ACG Thr	Trp	Ser	Сув 150	Ala	Ala	Pro	Thr	Arg 155	Ser	*	Arg	Asp	478
Ser 160	Pro	Ala		Leu	Ile 165	Leu	Ser	*	Thr	Ala 170	Thr	Pro	Pro	Ser	Leu 175	526
Arg	Arg	Trp	ACT Thr	Ser 180	Val	Trp	Ile	Pro	Leu 185	Leu	Pro	Leu	Arg	Leu 190	Pro	574
Gln	Cys	Pro	AGG Arg 195	Thr	Gln	Cys	Pro	Glu 200	Ala	Ser	Val	Gly	Ala 205	Ala	Arg	622
Gly	Glu	Val 210	GGC	Thr	Ala	Tyr	Thr 215	Gly	Met	Ser	Arg	Leu 220	Glu	Arg	Asp	670
CGT	CTG Leu	GCA Ala	TGT Cys	TCG Ser	ACT Thr	CCG Pro	TGG Trp	TGC Cys	TCT Ser	GTG Val	AGT Ser	GCT Ala	ACG Thr	ATG Met	CCG Pro	718

WO 94/25601	•	251	·	PCT/EP94/01323
		231		

		251		,
225	230	:	235	
		CTC CTG CCG AGA ( Leu Leu Pro Arg ) 250		
		GCT CCC TGT CTG : Ala Pro Cys Leu : 265		
	y Gly Val His	GGG GCT CAC TAA ( Gly Ala His * 1 280		
GCT GTC ACA GA Ala Val Thr As 290	C CAA ACA GGG p Gln Thr Gly	TGG GGA GAA TTT ( Trp Gly Glu Phe I 295	CCC ATA CCT TGT Pro Ile Pro Cys 300	AGC 910 Ser
		TCG CGC GAA AGC C Ser Arg Glu Ser A		
		GCT CCG TCT CAA A Ala Pro Ser Gln T 330	Thr Asp Leu Thr	
CCT ACT CCC CT Pro Thr Pro Le	C TTG TAC AGG u Leu Tyr Arg 340	CTG GGG CCC GTC C Leu Gly Pro Val G 345	CAG AAT GAG ATC . Sln Asn Glu Ile '	ACA 1054 Thr
CTG ACG CAC CC Leu Thr His Pr 35	o Ile Thr Lys	TAC ATT ATG GCT T Tyr Ile Met Ala C 360	TGC ATG TCT GCG ( Tys Met Ser Ala ) 365	GAC 1102 Asp
TTG GAG GTC AT Leu Glu Val Il 370	e Thr Ser Thr	TGG GTT CTG GTG G Trp Val Leu Val G 375	GGG GGC GTT GTG ( Sly Gly Val Val ( 380	GCG 1150 Ala
GCC CTG GCG GC Ala Leu Ala Al 385	C TAC TGC TTG a Tyr Cys Leu 390	ACG GTG GGT TCG G Thr Val Gly Ser V 3	STA GCC ATA GTC ( /al Ala Ile Val ( 195	GGT 1198 Gly
Arg Ile Ile Le 400	u Ser Gly Lys 405	CCT GCC ATC ATT C Pro Ala Ile Ile P 410	Pro Asp Arg Glu Y	Val 415
TTA TAC CAG CA Leu Tyr Gln Gli	A TTT GAT GAG n Phe Asp Glu : 420	ATG GAG GAG TGC T Met Glu Glu Cys S 425	CCG GCC TCG TTG ( er Ala Ser Leu 1 430	CCC 1294 Pro
	Thr Arg Ala	ATT GCC GGA CAA T Ile Ala Gly Gln P 440		
	Ser Thr Thr	GGC CAG AAG GCT G Gly Gln Lys Ala G 455		

WO 94/25601 PCT/EP94/01323

GCA GCC ACG TCT GTG TGG AAC AAG GCT GAG CAG TTC TGG CCA CAT ACA
Ala Ala Thr Ser Val Trp Asn Lys Ala Glu Gln Phe Trp Pro His Thr
465 470

TGT GGA ACT TCA TCA GTG GGA TAC AAT AAT AG
Cys Gly Thr Ser Ser Val Gly Tyr Asn Asn
480
485

1438

# (2) INFORMATION FOR SEQ ID NO: 197:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1485 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA

#### (ix) FRATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1485

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

TGTGCCAGGA CCATCA	CCAC CGGAGCTTCT	ATCACATACT	CCACTTACGG	CAAGTTCCTT	60
GCTGATGGAG GGTGTT	CAGG CGGCGCGCAT	GACGTGATCA	TATGCGACGA	GTGCCATTCC	120
CAGGACGCCA CCACCA	TTCT TGGGATAGGC	ACTGTCCTTG	ACCAGGCAGA	GACGGCTGGA	180
GCTAGGCTCG TCGTCT	IGGC CACGGCCACC	CCTCCCGGCA	GTGTGACAAC	GCCCCACCCC	240
AACATCGAGG AAGTGG	CCCT GCCTCAGGAG	GGGGAGGTTC	CCTTCTACGG	CAGAGCCATT	300
CCCCTTGCTT TTATAA	AGGG TGGTAGGCAT	CTCATCTTCT	GCCATTCCAA	GAAAAAATGT	360
GATGAACTCG CCAAGC	AACT GACCAGCCTG	GGCGTGAACG	CCGTGGCATA	TTATAGAGGT	420
CTAGACGTCG CCGTCAT	FACC CACAACAGGA	GACGTGGTCG	TGTGCAGCAC	CGACGCGCTC	480
ATGACGGGAT TCACCGG	CGA CTTTGATTCT	GTCATAGACT	GCAACTCCGC	CGTCACTCAG	540
ACGGTGGACT TCAGTCT	rgga teccaetttt	ACCATTGAGA	CTACCACAGT	GCCCCAGGAC	600
GCAGTGTCCA GAAGCC	AGCG TTGGGGCCGC	ACGGGGAGAG	GTAGGCACGG	CATATACCGG	660
TATGTCTCGG CTGGAGA	GAG ACCGTCTGGC	ATGTTCGACT	CCGTGGTGCT	CTGTGAGTGC	720
TACGATGCCG GATGTGC	ATG GTACGATCTG	ACTCCTGCCG	AGACTACCGT	GAGGTTGCGC	780
GCTTACNTAA ACACCCC	CGG GCTCCCTGTC	TGTCAGGACC	ATTTGGAATT	CTGGGAGGGG	840
GTGTTCACGG GGCTCAC	TAA CATCGACGCT	CACATGCTGT	CACAGACCAA	ACAGGGTGGG	900
GAGAATTTCC CATACCT	TGT AGCGTACCAA	GCAACAGTCT	GTGTTCGCGC	GAAAGCGCCC	960 ·

WO 94/25601 . PCT/EP94/01323

253

CCCCCCAGCT	GGGACACAAT	GTGGAAATGC	ATGCTCCGTC	TCAAACCGAC	NTTAACTGGC	1020
CCTACTCCCC	TCTTGTACAG	GCTGGGGCCC	GTCCAGAATG	AGATCACACT	GACGCACCCC ·	1080
ATCACCAAGT	ACATTATGGC	TTGCATGTCT	GCGGACTTGG	AGGTCATTAC	CAGCACTTGG	1140
GTTCTGGTGG	GGGGCGTTGT	GGCGGCCCTG	GCGGCCTACT	GCTTGACGGT	GGGTTCGGTA	1200
GCCATAGTCG	GTAGGATCAT	CCTCTCTGGG	AAACCTGCCA	TCATTCCCGA	TAGGGAGGTA	1260
TTATACCAGC	AATTTGATGA	GATGGAGGAG	TGCTCGGCCT	CGTTGCCCTA	TATGGACGAA	1320
ACACGTGCCA	TTGCCGGACA	ATTCAAAGAG	AAAGTGCTCG	GCTTCATCAG	CACGACCGGC	1380
CAGAAGGCTG	AAACTCTGAA	GCCGGCAGCC	ACGTCTGTGT	GGAACAAGGC	TGAGCAGTTC	1440
TGGNCCACAT	ACATGTGGAA	CTTCATCAGT	GGGATACAAT	AATAG		1485

#### (2) INFORMATION FOR SEQ ID NO: 198:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 484 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Cys Ala Arg Thr Ile Thr Thr Gly Ala Ser Ile Thr Tyr Ser Thr Tyr

1 10 15

Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala His Asp Val 20 25 30

Ile Ile Cys Asp Glu Cys His Ser Gln Asp Ala Thr Thr Ile Leu Gly
35 40 45

Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val 50 55 60

Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Thr Pro His Pro 65 70 75 80

Asn Ile Glu Glu Val Ala Leu Pro Gln Glu Gly Glu Val Pro Phe Tyr 85 90 95

Gly Arg Ala Ile Pro Leu Ala Phe Ile Lys Gly Gly Arg His Leu Ile 100 105 110

Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Lys Gln Leu Thr 115 120 125

Ser Leu Gly Val Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ala 130 135 140

Val Ile Pro	Thr Thr Gly As	sp Val Val Val Cys Ser	Thr Asp Ala Leu
145	150	<b>15</b> 5	160

254

Met Thr Gly Phe Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Ser 165 170 175

Ala Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile 180 185 190

Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Trp
195 200 . 205

Gly Arg Thr Gly Arg Gly Arg His Gly Ile Tyr Arg Tyr Val Ser Ala 210 215 220

Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Val Val Leu Cys Glu Cys 225 230 235 240

Tyr Asp Ala Gly Cys Ala Trp Tyr Asp Leu Thr Pro Ala Glu Thr Thr 245 250 255

Val Arg Leu Arg Ala Tyr Xaa Asn Thr Pro Gly Leu Pro Val Cys Gln 260 265 270

Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr Asn Ile 275 280 . 285

Asp Ala His Met Leu Ser Gln Thr Lys Gln Gly Glu Asn Phe Pro 290 295 300

Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Val Arg Ala Lys Ala Pro 305 310 315 320

Pro Pro Ser Trp Asp Thr Met Trp Lys Cys Met Leu Arg Leu Lys Pro

Xaa Leu Thr Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Pro Val Gln 340 345 350

Asn Glu Ile Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys 355 360 365

Met Ser Ala Asp Leu Glu Val Ile Thr Ser Thr Trp Val Leu Val Gly 370 375 380

Gly Val Val Ala Ala Leu Ala Ala Tyr Cys Leu Thr Val Gly Ser Val 385 390 395 400

Ala Ile Val Gly Arg Ile Ile Leu Ser Gly Lys Pro Ala Ile Ile Pro 405 410 415

Asp Arg Glu Val Leu Tyr Gln Gln Phe Asp Glu Met Glu Glu Cys Ser 420 " 425 430

Ala Ser Leu Pro Tyr Met Asp Glu Thr Arg Ala Ile Ala Gly Gln Phe
435 440 445

WO 94/25601 PCT/EP94/01323

Lys Glu Lys Val Leu Gly Phe Ile Ser Thr Thr Gly Gln Lys Ala Glu 450 455 460

Thr Leu Lys Pro Ala Ala Thr Ser Val Trp Asn Lys Ala Glu Gln Phe 465 470 475 480

Trp Xaa Thr Tyr

### (2) INFORMATION FOR SEQ ID NO: 199:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1485 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA

#### (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1485

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

TGTGCCAGGA	CCATCACCAC	CGGAGCTTCT	ATCACATACT	CCACTTACGG	CAAGTTCCTT	60
GCTGATGGAG	GGTGTTCAGG	CGGCGCGTAT	GACGTGATCA	TATGCGACGA	GTGCCATTCC	120
CAGGACGCCA	CCACCATTCT	TGGGATAGGC	ACTGTCCTTG	ACCAGGCAGA	GACGGCTGGA	180
GCTAGGCTCG	TCGTCTTGGC	CACGGCCACC	CCTCCCGGCA	GTGTGACAAC	GCCCCACCCC	240
AACATCGAGG	AAGTGGCCCT	GCCTCAGGAG	GGGGAGGTTC	CCTTCTACGG	CAGAGCCATT	300
CCCCTTGCTT	TTATAAAGGG	TGGTAGGCAT	CTCATCTTCT	GCCATTCCAA	GAAAAAATGT	360
GATGAACTCG	CCAAGCAACT	GACCAGCCTG	GGCGTGAACG	CCGTGGCATA	TTATAGAGGT	420
CTAGACGTCG	CCGTCATCCC	CACAGCAGGA	GACGTGGTCG	TGTGCAGCAC	CGACGCGCTC	480
ATGACGGGAT	TCACCGGCGA	CTTTGATTCT	GTCATAGACT	GCAACTCCGC	CGTCACTCAG	540
ACGGTGGACT	TCAGTCTGGA	TCCCACTTTT	ACCATTGAGA	CTACCACAGT	GCCCCAGGAC	600
GCAGTGTCCA	GAAGCCAGCG	TAGGGGCCGC	ACGGGGAGAG	GTAGGCACGG	CATATACCGG	660
TATGTCTCGG	CTGGAGAGAG	ACCNTCTGAC	ATGTTCGACT	CCGTGGTGCT	CTGTGAGTGC	720
TACGATGCCG	GATGTGCGTG	GTATGATCTG	ACTCCTGCCG	AGACTACCGT	GAGGTTGCGC	780
GCTTACATAA	ACACCCCCGG	GCTCCCTGTC	TGTCAGGACC	ATTTGGAATT	CTGGGAGGG	840
GTGTTCACGG	GGCTCACTAA	CATCGACGCT	CACATGCTGT	CACAGACCAA	ACAGGGTGGG	900
GAGAATTTNC	CATACCTTGT	AGCGTACCAA	GCAACAGTCT	GTGTTCGCGC	GAAAGCGCCC	960

CCCCCAC	CT G	GGAC	ACAA	T GI	GGAA	ATGC	ATG	CTCC	GTC	TCAA	ACCG	AC 1	TTAA	.CTGG	c	1020
CCTACTC	CCC 1	CTT	TACA	G GC	TGGG	GCCC	GTC	CAGA	NTG	AGAT	CACA	CT G	ACGC	ACCC	C	1080
ATCACCAZ	AGT A	CATI	ATGG	C TI	GCAT	GTCI	GCG	GACT	TGG	AGGT	CATT	AC C	ANCA	CITG	G .	1140
GTTCTGGT	rgg g	GGGC	GTTG	T GG	CGGC	CCTG	·GCG	GCCT	ACT	GCTT	GACG	GT G	GGTT	CGGT	Α	1200
GCCATAGT	cc c	TAGG	ATCA	T CC	TCTC	TGGG	AAA	.CCTG	CCA	TCAT	TCCC	ga T	'AGGG	AGGC	A	1260
TTATACCA	GC A	ATTT	GATG	A GA	TGGA	.GGAG	TGC	TCGG	CCT	CGTT	GCCC	TA T	'ATGG	ACGA	G	1320
ACACGTGC	CA T	TGCC	GGAC	A AT	TCAA	AGAG	AAA	GTGC	TCG	GCTT	CATC	AG C	ACGA	CCGG	C	1380
CAGAAGGC	TG A	AACT	CTGA	A GC	CGGC	AGCC	ACG	TCTG	TGT	GGAA	CAAG	GC T	GAGC	AGTT	С	1440
TGGGCCAC	AT A	CATG	TGGA	A CT	TCAT	CAGC	GGG	ATAC	AAT	AATA	G			-		1485
(ii)	SEQ (A (B (C (D	UENC ) LE ) TY ) ST ) TO	FOR E CH NGTH PE: RAND POLO E TY	ARAC: 48 amin EDNE GY:	TERI 4 am o ac SS: line prot	STIC ino id sing ar ein	S: acid le		: 20	0:						
Cys 1	Ala	Arg	Thr	Ile 5	Thr	Thr	Gly	Ala	Ser 10	Ile	Thr	Tyr	Ser	Thr 15	•	
Gly	Lys	Phe	Leu 20	Ala	Asp	Gly	Gly	Cys 25	Ser	Gly	Gly	Ala	Tyr 30	Авр	Val	
Ile	Ile		Asp							Ala				Leu	Gly	
Ile	Gly 50	Thr	Val	Leu	Asp	Gln 55	Ala	Glu	Thr	Ala	Gly 60	Ala	Arg	Leu	Val	
Val 65	Leu	Ala	Thr	Ala	Thr 70	Pro	Pro	Gly	Ser	Val 75	Thr	Thr	Pro	His	Pro 80	
Asn	Ile	Glu	Glu	Val 85	Ala	Leu	Pro	Gln	Glu 90	Gly	Glu	Val	Pro	Phe 95	Tyr	
Gly	Arg	Ala	Ile 100	Pro	Leu	Ala 	Phe	Ile 105	Lys	Gly	Gly	Arg	His 110	Leu	Ile	
Phe	Cys	His 115	Ser	Lys	Lys	Lys	Cys 120	Asp	Glu	Leu	Ala	Lys 125	Gln	Leu	Thr	

256

PCT/EP94/01323

WO 94/25601

125

							257								
Ser	130	u Gl	y Vai	l Ası	n Ala	Va]		Туг	Tyr	Arg	Gly 140		Asp	Val	Ala
Val 145		e Pro	Th:	r Ala	150		Val	Val	Val	Cys 155		Thr	Asp	Ala	Leu 160
Met	Thi	Gly	Phe	Th:	Gly	Asp	Phe	Asp	Ser 170		Ile	Asp	Cys	Asn 175	Ser
Ala	Va]	l Thi	Glr 180		Val	Asp	Phe	Ser 185		Asp	Pro	Thr	Phe 190		Ile
Glu	Thr	Thr 195	Thr	Val	. Pro	Gln	Asp 200	Ala	Val	Ser	Arg	Ser 205	Gln	Arg	Arg
Gly	Arg 210		Gly	/ Arg	Gly	Arg 215	His	Gly	Ile	Tyr	Arg 220	Tyr	Val	Ser	Ala
Gly 225		Arg	Xaa	Ser	230	Met	Phe	Asp	Ser	Val 235	Val	Leu	Cys	Glu	Cys 240
Tyr	Asp	Ala	Gly	Cys 245		Trp	Tyr	Asp	Leu 250	Thr	Pro	Ala	Glu	Thr 255	Thr
Val	Arg	Leu	Arg 260		Tyr	Ile	Asn	Thr 265	Pro	Gly	Leu	Pro	Val 270	_	Gln
<b>Asp</b>	His	<b>Leu</b> 275		Phe	Trp	Glu	Gly 280	Val	Phe	Thr	Gly	Leu 285	Thr	Asn	Ile
Asp	Ala 290		Met	Leu	Ser	Gln 295	Thr	Lys	Gln	Gly	Gly 300	Glu	Asn	Xaa	Pro
Tyr 305	Leu	Val	Ala	Tyr	Gln 310	Ala	Thr	Val	Cys	Val 315	Arg	Ala	Lys	Ala	Pro 320
Pro	Pro	Ser	Trp	Asp 325	Thr	Met	Trp	Lys	Суз 330	Met	Leu	Arg	Leu	Lys 335	Pro
Thr	Leu	Thr	Gly 340	Pro	Thr	Pro	Leu	Leu 345	Tyr	Arg	Leu	Gly	Pro 350	Val	Gln
Xaa	Glu	Ile 355	Thr	Leu	Thr	His	Pro 360	Ile	Thr	Lya	Tyr	Ile 365	Met	Ala	Сув
Met	Ser 370	Ala	Asp	Leu	Glu	Val 375	Ile	Thr	Xaa	Thr	Trp 380	Val	Leu	Val	Gly
385					390	٠	Ala			395					400
				405			Leu		410					415	
			420					425					430	Cys	Ser
Ala	Ser	T.em	Pro	Tvr	Mot	Aen	Glu.	m>	3	21-	T1 -		<b>~1</b>	<b>~</b> 3	m1 -

258

435

440

445

Lys Glu Lys Val Leu Gly Phe Ile Ser Thr Thr Gly Gln Lys Ala Glu
450 455 460

Thr Leu Lys Pro Ala Ala Thr Ser Val Trp Asn Lys Ala Glu Gln Phe 465 470 475 480

Trp Ala Thr Tyr

- (2) INFORMATION FOR SEQ ID NO: 201:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..340
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 2..337
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

C TCC	ACT	GTG	ACT	GAG	AGA	GAC	ATC	AGG	GTC	GAA	GAA	GAA	GTC	TAT	46
Ser	Thr	Val	Thr	Glu	Arg	Asp	Ile	Arg	Val	Glu	Glu	Glu	Val	Tvr	40
1				5				_	10					15	

CAG TGT TGT GAT CTG GAG CCC GAG GCC CGC AAG GTA ATA ACC GCC CTC
Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Thr Ala Leu
20 25 30

ACG GAG AGA CTC TAC GTG GGC GGC CCT ATG TAC AAT AGC AAG GGA GAC
Thr Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp
35
40

CTT TGC GGG TAT CGC AGG TGC CGC GCA AGC GGC GTA TAT ACC ACC AGC
Leu Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser
50 55 60

TTC GGG AAC ACA CTG ACG TGC TAC CTT AAA GCC TCA GCA GCC ATC AGG
Phe Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg
65 70 ... 75

GCT GCG GGG CTG AAG GAC TGC ACC ATG CTG GTT TGC GGT GAC GAC TTA
Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu
80 85 90 95

WO 94/25601 . PCT/EP94/01323

259

GTC GTG ATC GCT GAA AGC GGT GGC GTC GAG GAG GAC AAG CGA GCC CTC 334
Val Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu
100 105 110

GGA GCT

340

Gly Ala

(2) INFORMATION FOR SEQ ID NO: 202:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:

Ser Thr Val Thr Glu Arg Asp Ile Arg Val Glu Glu Glu Val Tyr Gln

1 5 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Thr Ala Leu Thr

Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp Leu
35 40

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 60

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Ile Arg Ala 65 70 75 80

Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Lys Arg Ala Leu Gly 100 105 110

Ala

- (2) INFORMATION FOR SEQ ID NO: 203:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO

(ix) FEATURE:

238

		(	A) N	AME/	KEY:	CDS										
		(	B) L	OCAT	ION:	2	340			٠						
	(ix	) FE	ATUR	E:												
		(.	A) N	AME/	KEY:	mat	рер	tide								
					ION:											
	(xi	) SE	QUEN	CE D	ESCR	IPTI	ON:	SEQ	ID N	0: 2	03:					
СТ	CC A	CA G	TG A	CT G	AA A	GA G	AC A	TC A	GG G'	TC G	AG G	AA G	אם פ	ጥር ጥ	אר	46
s	er T	hr Va	al T	hr G	lu A	rg A	sp I	le A	rg Va	al G	lu G	lu G	lu V	al T	vr	40
	1				5		-			10					15	
~~																
CAG	TGT	TGT	GAC	CIG	GAG	CCT	GAA	ACC	CGC	AAG	GTA	ATA	TCT	GCC	CTC	94
GIII	Cys	Cys	Asp		Glu	Pro	GIu	Thr		Lys	Val	Ile	Ser	Ala	Leu	
				20					25					30		
ACT	GAA	AGA	CTC	TAT	GTG	GGC	GGT	ccc	ATG	CAC	AAC	AGC	AGG	GGA	GAC	142
Thr	Glu	Arg	Leu	Tyr	Val	Gly	Gly	Pro	Met	His	Asn	Ser	Ara	Glv	Agn	142
			35	•		•	•	40					45	017	-mp	
CTA	TGC	GGG	TAC	CGT	AGA	TGC	CGC	GCG	AGC	GGC	GTA	TAC	ACC	ACA	AGC	190
Leu	Суз	Gly	Tyr	Arg	Arg	Сув	Arg	Ala	Ser	Gly	Val	Tyr	Thr	Thr	Ser	
		50					55									

GCC GCT GGC CTA AAG GAC TGC ACC ATG TTG GTG TGT GGT GAC GAC TTA 286 Ala Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 85

TTC GGG AAC ACT CTG ACG TGC TTC CTC AAG GCC ACA GCG GCC ACC AAA

Phe Gly Asn Thr Leu Thr Cys Phe Leu Lys Ala Thr Ala Ala Thr Lys

70

GTC GTT ATC GCC GAA AGC GAT GGT GTC GAA GAG GAC CGC CGA GCC CTC 334 Val Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Arg Arg Ala Leu 100

GGA GCT 340 Gly Ala

- (2) INFORMATION FOR SEQ ID NO: 204:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 113 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

Ser Thr Val Thr Glu Arg Asp Ile Arg Val Glu Glu Glu Val Tyr Gln 1 5

WO 94/25601 . PCT/EP94/01323

Cys Cys Asp Leu Glu Pro Glu Thr Arg Lys Val Ile Ser Ala Leu Thr
20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Arg Gly Asp Leu 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 55

Gly Asn Thr Leu Thr Cys Phe Leu Lys Ala Thr Ala Ala Thr Lys Ala
.65 70 75 80

Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ala Glu Ser Asp Gly Val Glu Glu Asp Arg Arg Ala Leu Gly
100 105 110

Ala

#### (2) INFORMATION FOR SEQ ID NO: 205:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 340 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 2..340
- (ix) FEATURE:
  - (A) NAME/KEY: mat\_peptide
  - (B) LOCATION: 2..337
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

C TCC ACG GTG ACC GAA AGG GAT ATC AGG ACC GAG GAA GAG ATC TAC

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Glu Ile Tyr

1 5 10 15

CAG TGC TGC GAC CTG GAG CCC GAA GCC CGC AAG GTG ATA TCC GCC CTA

Gln Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ala Leu

20 25 30

ACG GAA AGA CTC TAC GTG GGC GGT CCC ATG TAC AAC TCC AAG GGG GAC

Thr Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp

35

40

45

WO 94/25601 PCT/EP94/01323

262

		CGG Arg							190
		GTA Val					 		238
		AAA Lys							286
		GAG Glu 100							334
CGA Arg									340

- (2) INFORMATION FOR SEQ ID NO: 206:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 113 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Glu Ile Tyr Gln
1 5 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ala Leu Thr
20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp Leu 35 40

Cys Gly Gln Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 55 60

Gly Asn Thr Val Thr Cys Tyr Leu Lys Ala Val Ala Ala Thr Arg Ala 65 70 75 80

Ala Gly Leu Lys Gly Cys Ser Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Cys Glu Ser Gly Gly Val Glu Glu Asp Ala Arg Ala Leu Arg 100 105 110

Ala

(2) INFORMATION FOR SEQ ID NO: 207:

340

WU 94/25601	<b>263</b>	PCT/EP94/01323
(i)	SEQUENCE CHARACTERISTICS:  (A) LENGTH: 340 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii)	MOLECULE TYPE: cDNA	
(iii)	HYPOTHETICAL: NO	
(iii)	ANTI-SENSE: NO	
(ix)	FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 2340	
(ix)	FEATURE:	•
	(A) NAME/KEY: mat_peptide (B) LOCATION: 2337	
(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 2	07:
C TCC ACG Ser Thr 1	GTG ACT GAA AGG GAC ATT AGG GTC G Val Thr Glu Arg Asp Ile Arg Val G 5	AG GAA GAG ATC TAC 46 lu Glu Glu Ile Tyr 15
CAG TGC TG Gln Cys C	GT GAC CTG GAG CCC GAG GCA CGC AAG /s Asp Leu Glu Pro Glu Ala Arg Lys 20 25	GTG ATA TCC GCT CTC 94 Val Ile Ser Ala Leu 30
ACA GAA AG	SA CTC TAC AAG GGC GGC CCC ATG TAT	AAC AGC AAG GGG GAC 142
	rg Leu Tyr Lys Gly Gly Pro Met Tyr 35 40	45
ren cas Ci	GG CTT CGG AGG TGC CGC GCA AGC GGG y Leu Arg Arg Cys Arg Ala Ser Gly 55	GTA TAC ACC ACA AGC 190 Val Tyr Thr Thr Ser 60
TTC GGG AF	C ACG GTG ACA TGC TAC CTT AAA GCC n Thr Val Thr Cys Tyr Leu Lys Ala	ACA GCA GCC ACC AGG 238 Thr Ala Ala Thr Arg
65	. 70	75
GCT GCA GG Ala Ala Gl 80	G CTG AAA GAT TGC ACT ATG CTG GTA y Leu Lys Asp Cys Thr Met Leu Val 85 90	TGC GGT GAC GAC TTA 286 Cys Gly Asp Asp Leu 95
GTC GTT AT Val Val Il	T GCC GAA AGC GGT GGC GTG GAG GAG e Ala Glu Ser Gly Gly Val Glu Glu 100 105	GAC GCC CGA GCC CTC 334 Asp Ala Arg Ala Leu 110

(2) INFORMATION FOR SEQ ID NO: 208:

CGA GCC

Arg Ala

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:

Ser Thr Val Thr Glu Arg Asp Ile Arg Val Glu Glu Glu Ile Tyr Gln
1 5 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ala Leu Thr 20 25 30

Glu Arg Leu Tyr Lys Gly Gly Pro Met Tyr Asn Ser Lys Gly Asp Leu 35 40 45

Cys Gly Leu Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 50 55 60

Gly Asn Thr Val Thr Cys Tyr Leu Lys Ala Thr Ala Ala Thr Arg Ala 65 70 75 80

Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ala Glu Ser Gly Gly Val Glu Glu Asp Ala Arg Ala Leu Arg 100 105 110

Ala

- (2) INFORMATION FOR SEQ ID NO: 209:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..340
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 209:

CCCCACCGTG ACNGAGAGGG ACNTCAGGGT CGAGGAAGAG GTCTATCAGT GCTGTAATCT

60

GGAGNCCGAT GNCCGCAAGG TCATCAACGC CCTCACAGAG AGACTCTACG TGGGCGGCCC

) 94/25601 265	PCT/EP94/01323				
TATGCACAAC AGCAAGGGAG ACCTGTGTGG CAT	CCGTAGA TGCCGCGCGA (	GCGGCGTTTA 180			
CACCACGAGC TTCGGAAACA CGCTGACTTG CTA	CCTCAAA GCCACAGCGG (	CCACCAGGGC 240			
CGCGGGCTTG AAGGATTGCA CCATGCTGGT CTG	CGGNGAC GACCTGGTTG	CATTGCTGA 300			
GAGCATTGGC ATAGACGAGG ACAAGCAAGC CCT	CCGNACT	340			
(2) INFORMATION FOR SEQ ID NO: 210:	·				
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 113 amino acid  (B) TYPE: amino acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA  (iii) HYPOTHETICAL: NO  (iii) ANTI-SENSE: NO	3				
(xi) SEQUENCE DESCRIPTION: SEQ II	) NO: 210:				
Pro Thr Val Thr Glu Arg Asp Xaa	Arg Val Glu Glu Glu 10	Val Tyr Gln 15			
Cys Cys Asn Leu Glu Xaa Asp Xaa 20	Arg Lys Val Ile Asn 25	Ala Leu Thr			

Glu Arg Leu Tyr Val Gly Gly Pro Met His Asn Ser Lys Gly Asp Leu

Cys Gly Ile Arg Arg Cys Arg Ala Ser Gly Val Tyr Thr Thr Ser Phe 55

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Thr Ala Ala Thr Arg Ala 70

Ala Gly Leu Lys Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val

Val Ile Ala Glu Ser Ile Gly Ile Asp Glu Asp Lys Gln Ala Leu Arg

Thr

- (2) INFORMATION FOR SEQ ID NO: 211:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA

WO 94/25601 PCT/EP94/01323

(iii)	HYPOTHETICAL:	NO

(iii) ANTI-SENSE: NO

#### (ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..340

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:

CTCGACTGTG NCCGAGAGGG ACATCAGGAC AGAGGGAGAG GTCTATCAGT GTTGCGACCT 60

GGAACCGGAA GCCCGCAAGG TAATCACCGC CCTCACTGAG AGACTCTATG TGGGCGGACC 120

CATGTTCAAC AGCAAGGGAG ACCTGTGCGG ACAACGCCGG TGCCGCGCAA GCGGCGTGTT 180

CACCACCAGC TTCGGGAACA CACTGACGTG CTACCTTAAA GCCACAGCTG CTACTAGAGC 240

AGCCGGCTTA AAAGATTGCA CCATGCTGGT CTGCGGTGAC GACTTAGTCG TTATTTCCGA 300

GAGCGCCGGT GTGGAGGAGG ATCCCANAAC CCNNCGACCN 340

#### (2) INFORMATION FOR SEQ ID NO: 212:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (iii) ANTI-SENSE: NO

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:

Ser Thr Val Xaa Glu Arg Asp Ile Arg Thr Glu Gly Glu Val Tyr Gln

1 10 15

Cys Cys Asp Leu Glu Pro Glu Ala Arg Lys Val Ile Thr Ala Leu Thr 20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met Phe Asn Ser Lys Gly Asp Leu 35 40 45

Cys Gly Gln Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser Phe 50 55 60

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Thr Ala Ala Thr Arg Ala

WO 94/25601					267			PCT/E	P94/01323
65			70	)		7	5		80
Ala	Gly L	eu Lys	Asp Cy 85	s Thr	Met Le	val C	ys Gly <i>I</i>	Asp Asp Leu 95	Val
Val	Ile S	er Glu 100	Ser Al	a Gly	Val Glu 10		sp Pro }	(aa Thr Xaa 110	Arg
Pro									
(2) INFO	RMATIO	N FOR S	SEQ ID	NO: 21	3:				
(i)	(A) I (B) I (C) S	ENGTH: TYPE: r	340 h nucleic DNESS:	single	irs				
(ii)	MOLECT	TE TYP	E: cDN	À					
(iii)	HYPOTE	ETICAL	: NO						
(iii)	ANTI-S	ense :	NO					,	
(ix)		e: Ame/ke Ocatio							·
(ix)	FEATUR (A) N (B) L		Y: mat N: 2	_peption	le				
(xi)	SEQUEN	CE DES	CRIPTI	ON: SEQ	) ID NO	: 213:			
C TCA ACA Ser Thr	GTC A	CC GAG hr Glu 5	AAC G Asn A	AC ATC sp Ile	CGT GT Arg Va 1	l Glu G	AG TCA . lu Ser	ATT TAC Ile Tyr 15	46
CAA TGT TGIN CYS C									94
ACA GAG Co	GG CTT rg Leu 35	Tyr I	rc GGG le Gly	Gly Pr	C CTG . O Leu '	ACT AAT Thr Asn	TCA AA Ser Ly:	s Gly Gln	142
AAC TGT GG Asn Cys G									190

TGC GGT AAT ACC CTT ACA TGT TAC"CTA AAG GCC TCT GCA GCC TGT CGA

Cys Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Cys Arg

GCT GCG AAG CTC CAG GAC TGC ACG ATG CTC GTG TGC GGG GAC GAC CTT

70

65

60

238

286

WO 94/25601 PCT/EP94/01323

268

Ala Ala Lys Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu 80 85 90 95

CGA GTC 340
Arg Val

- (2) INFORMATION FOR SEQ ID NO: 214:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 113 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:

Ser Thr Val Thr Glu Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln
1 5 10 15

Cys Cys Asp Leu Ala Pro Glu Ala Arg Gln Ala Ile Lys Ser Leu Thr 20 25 30

Glu Arg Leu Tyr Ile Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys 50 55 60

Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Cys Arg Ala 65 70 75 80

Ala Lys Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Cys Glu Ser Ala Gly Thr Gln Glu Asp Ala Ala Ser Leu Arg 100 105 110

Val

- (2) INFORMATION FOR SEQ ID NO: 215:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid(C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA

WO 94/25601 . PCT/EP94/01323

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 2..340

(ix) FEATURE:

•

(A) NAME/KEY: mat\_peptide
(B) LOCATION: 2..340

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

C TCA ACC GTC ACG GAG AGG GAT ATA AGA ACA GAA GAA TCC ATA TAT

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Ser Ile Tyr

1 5 10 15

CAA GCT TGT TCC CTG CCC CAA GAG GCC AGA ACT GTC ATA CAC TCG CTC 94
Gln Ala Cys Ser Leu Pro Gln Glu Ala Arg Thr Val Ile His Ser Leu
20 25 30

ACC GAG AGA CTC TAC GTG GGA GGG CCC ATG ATA AAC AGC AAA GGG CAA

Thr Glu Arg Leu Tyr Val Gly Gly Pro Met Ile Asn Ser Lys Gly Gln

35

40

45

TCC TGC GGT TAC AGG CGT TGC CGC GCA AGC GGT GTT TTC ACC ACC AGC

Ser Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser

50 55 60

ATG GGG AAT ACC ATG ACG TGT TAC ATC AAA GCC CTT GCA GCG TGT AAA

Met Gly Asn Thr Met Thr Cys Tyr Ile Lys Ala Leu Ala Ala Cys Lys

65 70 75

GCC GCA GGG ATC GTG GAC CCC GTC ATG CTG GTG TGT GGA GAC GAC CTG
Ala Ala Gly Ile Val Asp Pro Val Met Leu Val Cys Gly Asp Asp Leu
80 85 90 95

GTC GTC ATC TCG GAG AGC CAG GGT AAC GAG GAG GAC GAG CGA AAC CTG
Val Val Ile Ser Glu Ser Gln Gly Asn Glu Glu Asp Glu Arg Asn Leu
100 105 110

AGA GCT 340 Arg Ala

(2) INFORMATION FOR SEQ ID NO: 216:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 113 amino acids

(B) TYPE: amino acid "

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:

Ser Thr Val Thr Glu Arg Asp Ile Arg Thr Glu Glu Ser Ile Tyr Gln
1 5 10 15

Ala Cys Ser Leu Pro Gln Glu Ala Arg Thr Val Ile His Ser Leu Thr
20 25 30

Glu Arg Leu Tyr Val Gly Gly Pro Met Ile Asn Ser Lys Gly Gln Ser 35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Phe Thr Thr Ser Met
50 55 60

Gly Asn Thr Met Thr Cys Tyr Ile Lys Ala Leu Ala Ala Cys Lys Ala 65 70 75 80

Ala Gly Ile Val Asp Pro Val Met Leu Val Cys Gly Asp Asp Leu Val 85 90 95

Val Ile Ser Glu Ser Gln Gly Asn Glu Glu Asp Glu Arg Asn Leu Arg
100 105 110

Ala

- (2) INFORMATION FOR SEQ ID NO: 217:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 340 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: cDNA
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 2..340
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 2..340
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:
- C TCG ACT GTC ACT GAA CAG GAC ATC AGG GTG GAA GAG GAG ATA TAT

  Ser Thr Val Thr Glu Gln Asp Ile Arg Val Glu Glu Glu Ile Tyr

  1 5 10 15

CAA TGC TGC AAC CTT GAA CCG GAG GCC AGG AAA GTG ATC TCC TCC CTC Gln Cys Cys Asn Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ser Leu

WO 94/25601			271		PCT/EP94/01323
	20	*		 _	

20 -25 30 ACG GAG CGG CTT TAC TGC GGA GGC CCT ATG TTT AAC AGC AAG GGG GCC 142 Thr Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly Ala 35 CAG TGT GGT TAT CGC CGT TGC CGT GCC AGT GGA GTT CTG CCT ACC AGC 190 Gln Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr Ser 50 TTT GGC AAC ACA ATC ACT TGT TAC ATC AAG GCC ACA ACG GCC GCG AAG 238 Phe Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Thr Ala Ala Lys 65 GCC GCA GGC CTC CGG AAC CCG GAC TTT CTT GTC TGC GGA GAT GAT CTG 286 Ala Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp Leu 80 90 GTC GTG GTG GCT GAG AGT GAT GGC GTC GAC GAG GAT AGA GCA GCC CTG 334 Val Val Val Ala Glu Ser Asp Gly Val Asp Glu Asp Arg Ala Ala Leu 100 105 AGA GCC 340 Arg Ala

### (2) INFORMATION FOR SEQ ID NO: 218:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 113 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:

Ser Thr Val Thr Glu Gln Asp Ile Arg Val Glu Glu Glu Ile Tyr Gln

1 5 10 15

Cys Cys Asn Leu Glu Pro Glu Ala Arg Lys Val Ile Ser Ser Leu Thr 20 25 30

Glu Arg Leu Tyr Cys Gly Gly Pro Met Phe Asn Ser Lys Gly Ala Gln
35 40 45

Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Pro Thr Ser Phe
50 55 60

Gly Asn Thr Ile Thr Cys Tyr Ile Lys Ala Thr Thr Ala Ala Lys Ala 65 70 75 80

Ala Gly Leu Arg Asn Pro Asp Phe Leu Val Cys Gly Asp Asp Leu Val
85 90 95

Val Val Ala Glu Ser Asp Gly Val Asp Glu Asp Arg Ala Ala Leu Arg

Ala

- (2) INFORMATION FOR SEQ ID NO: 219:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:

Arg Ser Glu Gly Arg Thr Ser Trp Ala Gln
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 220:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:

Arg Ser Glu Gly Arg Thr Ser Trp Ala Gln
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 221:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:

Arg Thr Glu Gly Arg Thr Ser Trp Ala Gln
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 222:
  - (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 629 base pairs

WO 94/25601 PCT/EP94/01323

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 3..629

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide

(B) LOCATION: 3..629

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:

TA	GAC Asp 1	TTT Phe	TGG Trp	GAG Glu	AGC Ser 5	GTC Val	TTC Phe	ACT Thr	GGA Gly	CTA Leu 10	ACT Thr	CAC His	ATA Ile	GAT Asp	GCC Ala 15	47
CAC	Phe	CTG Leu	TCA Ser	CAG Gln 20	Thr	AAG Lys	CAG Gln	CAG Gln	GGA Gly 25	Leu	AAC Asn	TTC Phe	TCG Ser	TTC Phe	CTG Leu	95
ACT Thr	GCC	TAC	CAA Gln 35	Ala	ACT Thr	GTG Val	TGC	GCT Ala 40	Arg	GCG	CAG Gln	GCI Ala	CCT Pro 45	Pro	CCA Pro	143
AGT Ser	TGG Trp	GAC Asp 50	Glu	ATG Met	TGG Trp	AAG Lys	TGT Cys 55	Leu	GTA Val	CGG	CTT	AAG Lys 60	Pro	ACA Thr	CTA Leu	191
CAT His	GGA Gly 65	CCT Pro	ACG Thr	CCT Pro	CTT Leu	CTA Leu 70	TAT Tyr	CGG Arg	TTG Leu	GGG Gly	CCT Pro 75	Val	CAA Gln	AAT Asn	GAA Glu	239
ATC Ile 80	TGC Cys	TTG Leu	ACA Thr	CAC His	CCC Pro 85	ATC Ile	ACA Thr	AAA Lys	TAC Tyr	ATC Ile 90	ATG Met	GCA Ala	TGC Cys	ATG Met	TCA Ser 95	287
GCT Ala	GAT Asp	CTG Leu	GAA Glu	GTA Val 100	ACC Thr	ACC Thr	AGC Ser	ACC Thr	TGG Trp 105	GTT Val	TTG Leu	CTT Leu	GGA Gly	GGG Gly 110	GTC Val	335
CTC Leu	GCG Ala	GCC Ala	CTA Leu 115	GCG Ala	GCC Ala	TAC Tyr	TGC Cys	TTG Leu 120	TCA Ser	GTC Val	GGT Gly	TGT Cys	GTT Val 125	GTG Val	ATT Ile	383
GTG Val	GGT Gly	CAT His 130	ATC Ile	GAG Glu	CTG Leu	GGG Gly	GGC Gly 135	AAG Lys	CCG Pro	GCA Ala	ATC Ile	GTT Val 140	CCA Pro	GAC Asp	AAA Lys	431

wo 9	4/256	01							274						PCT/	EP94/01323
GAG Glu	GTG Val 145	Leu	TAT Tyr	CAA Gln	CAA Gln	TAC Tyr 150	GAT Asp	GAG Glu	ATG Met	GAA Glu	GAG Glu 155	TGC Cys	TCA Ser	CAA Gln	GCT Ala	479
	Pro		ATC Ile													527
AAA Lys	GTC Val	CTT	GGA Gly	TTG Leu 180	CTG Leu	CAG Gln	CGA Arg	GCC Ala	ACC Thr 185	CAA Gln	CAA Gln	CAA Gln	GCT Ala	GTC Val 190	ATT Ile	575
			GTA Val 195													623
	CAT His															629
(2)	INF	ORMA'	TION	FOR	SEQ	ID 1	NO: :	223:	٠							
		(1	SEQUI A) LI B) TY	engti (PE :	H: 20	)9 ar	nino cid		•							
	(ii)	MO	LECUI	LE T	PE:	prot	cein									
	(xi)	SE	QUENC	E DI	ESCRI	PTIC	ON: S	SEQ :	ED NO	2: 2:	23:					
Asp 1	Phe	Trp	Glu	Ser 5	Val	Phe	Thr	Gly	Leu 10	Thr	His	Ile	Asp	Ala 15	His	
Phe	Leu	Ser	Gln 20	Thr	Lys	Gln	Gln	Gly 25	Leu	Asn	Phe	Ser	Phe 30	Leu	Thr	
Ala	Tyr	Gln 35	Ala •	Thr	Val	Сув	Ala 40	Arg	Ala	Gln	Ala	Pro 45	Pro	Pro	Ser	
Trp	Asp 50	Glu	Met	Trp	Lys	Суз 55	Leu	Val	Arg	Leu	Lys 60	Pro	Thr	Leu	His	
Gly 65	Pro	Thr	Pro	Leu	Leu 70	Tyr	Arg	Leu	Gly	Pro 75	Val	Gln	Asn	Glu	Ile 80	
Cys	Leu	Thr	His	Pro 85	Ile	Thr	Lys	Tyr	Ile 90	Met	Ala	Cys	Met	Ser 95	Ala	
Asp	Leu	Glu	Val 100	Thr	Thr	Ser	Thr	Trp 105	Val	Leu	Leu	Gly	Gly 110	Val	Leu	
Ala	Ala	Leu 115	Ala	Ala	Tyr	Cys	Leu 120	Ser	Val	Gly	Cys	Val 125	Val	Ile	Val	
Gly	His 130	Ile	Glu	Leu	Gly	Gly 135	Lys	Pro	Ala	Ile	Val 140	Pro	Asp	Lys	Glu	

Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu Cys Ser Gln Ala Ala 145 150 155 160

Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln Phe Lys Glu Lys 165 170 175

Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln Gln Ala Val Ile Glu 180 185 190

Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu Ala Phe Trp His Lys

His

- (2) INFORMATION FOR SEQ ID NO: 224:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (ix) FEATURE:
    - (A) NAME/KEY: Peptide
    - (B) LOCATION: 2..12
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:

Ile His Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 225:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

Val Asn Tyr Arg Asn Ala Ser Gly Ile Tyr His Ile 1 5

- (2) INFORMATION FOR SEQ ID NO: 5:
  - (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

Val Asn Tyr Arg Asn Ala Ser Gly Val Tyr His Ile 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 227:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

Val Asn Tyr His Asn Thr Ser Gly Ile Tyr His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 228:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:

Gln His Tyr Arg Asn Ala Ser Gly Ile Tyr His Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 229:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:

Gln His Tyr Arg Asn Val Ser Gly Ile Tyr His Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 230:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 230:

Ile His Tyr Arg Asn Ala Ser Asp Gly Tyr Tyr Ile

5 10

- (2) INFORMATION FOR SEQ ID NO: 231:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 12 amino acids
      - (B) TYPE: amino acid
      - (C) STRANDEDNESS: single
      - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 231:

Leu Gln Val Lys Asn Thr Ser Ser Ser Tyr Met Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 232:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 232:

Val Trp Gln Leu Arg Ala Ile Val Leu His Val 1 5 10

(2) INFORMATION FOR SEQ ID NO: 233:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 11 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 233:

Val Tyr Glu Ala Asp Tyr His Ile Leu His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 234:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 234:

Val Tyr Glu Thr Asp Asn His Ile Leu His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 235:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 235:

Val Tyr Glu Thr Glu Asn His Ile Leu His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 236:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid "
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 236:

Val Phe Glu Thr Val His His Ile Leu His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 237:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 237:

Val Phe Glu Thr Glu His His Ile Leu His Leu

1 5 10

- (2) INFORMATION FOR SEQ ID NO: 238:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 238:

Val Phe Glu Thr Asp His His Ile Met His Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 239:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 239:

Val Tyr Glu Thr Glu Asn His Ile Leu His Leu

1 5 10

- (2) INFORMATION FOR SEQ ID NO: 240:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 240:

Val Tyr Glu Ala Asp Ala Leu Ile Leu His Ala 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 241:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 241:

Val Gln Asp Gly Asn Thr Ser Ala Cys Trp Thr Pro Val 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 242:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
- (2) INFORMATION FOR SEQ ID NO: 243:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 243:

Val Lys Thr Gly Asn Gln Ser Arg Cys Trp Val Ala Leu

1 5 10

- (2) INFORMATION FOR SEQ ID NO: 244:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 244:

Val Arg Thr Gly Asn Gln Ser Arg Cys Trp Val Ala Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 245:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 245:

Val Lys Thr Gly Asn Gln Ser Arg Cys Trp Ile Ala Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 246:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 246:

Val Lys Thr Gly Asn Gln Ser Arg Cys Trp Ile Ala Leu

1

5

10

- (2) INFORMATION FOR SEQ ID NO: 247:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 247:

Val Lys Thr Gly Asn Ser Val Arg Cys Trp Ile Pro Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 248:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 248:

Val Lys Thr Gly Asn Val Ser Arg Cys Trp Ile Ser Leu 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 249:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 13 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 249:

Val Arg Lys Asp Asn Val Ser Arg Cys Trp Val Gln Ile 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 250:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 250:

Ala Pro Ser Phe Gly Ala Val Thr Ala Pro 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 251:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 251:

Val Ser Gln Pro Gly Ala Leu Thr Lys Gly
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 252:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 252:

Val Lys Tyr Val Gly Ala Thr Thr Ala Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 253:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 253:

Ala Pro Tyr Ile Gly Ala Pro Val Glu Ser
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 254:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 254:

Ala Gln His Leu Asn Ala Pro Leu Glu Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 255:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 255:

Ser Pro Tyr Val Gly Ala Pro Leu Glu Pro 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 256:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 256:

Ser Pro Tyr Ala Gly Ala Pro Leu Glu Pro 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 257:
  - (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 10 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 257:

Ala Pro Tyr Leu Gly Ala Pro Leu Glu Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 258:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 258:

Ala Pro Tyr Leu Gly Ala Pro Leu Glu Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 259:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 259:

Ala Pro Tyr Val Gly Ala Pro Leu Glu Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 260:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 11 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 260:

Asn Val Pro Tyr Leu Gly Ala Pro Leu Thr Ser
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 261:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 261:

Ala Pro His Leu Arg Ala Pro Leu Ser Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 262:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 262:

Ala Pro Tyr Leu Gly Ala Pro Leu Thr Ser 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 263:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 263:

Arg Pro Arg Gln His Ala Thr Val Gln Asp 1 5 10

(2) INFORMATION FOR SEQ ID NO: 264:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 10 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 264:

Ser Pro Gln His His Lys Phe Val Gln Asp 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 265:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 265:

Arg Pro Arg Arg Leu Trp Thr Thr Gln Glu
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 266:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 10 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 266:

Pro Pro Arg Ile His Glu Thr Thr Gln Asp 1 5 10

- (2) INFORMATION FOR SEQ ID NO: 267:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 14 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear

WO 94/25601 PCT/EP94/01323

288

- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 267:

Thr Ile Ser Tyr Ala Asn Gly Ser Gly Pro Ser Asp Asp Lys
1 5 10

- (2) INFORMATION FOR SEQ ID NO: 268:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 19 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: peptide
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 268:

Ser Arg Arg Gln Pro Ile Pro Arg Ala Arg Arg Thr Glu Gly Arg Ser 1 5 10 15

Trp Ala Gln

- (2) INFORMATION FOR SEQ ID NO: 269:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 1443 base pairs
    - (B) TYPE: nucleic acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: DNA (genomic)
  - (iii) HYPOTHETICAL: NO
  - (iii) ANTI-SENSE: NO
  - (ix) FEATURE:
    - (A) NAME/KEY: CDS
    - (B) LOCATION: 1..1443
  - (ix) FEATURE:
    - (A) NAME/KEY: mat\_peptide
    - (B) LOCATION: 1..1443
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 269:

ACC ATC ACC ACC GGA GCT TCT ATC ACA TAC TCC ACT TAC GGC AAG TTC
Thr Ile Thr Thr Gly Ala Ser Ile Thr Tyr Ser Thr Tyr Gly Lys Phe

WO 94/25601

PCT/EP94/01323

289

:	1			!	5				10	)				15	;	
CT	r GC	T GA' a As <sub>l</sub>	r GG/ p Gly 20	/ Gly	TG1	TCA Ser	GGC Gly	GGC Gly 25	, Ala	TAT	GAC Asp	GTG Val	Ile 30	Ile	TGC Cys	<b>96</b>
Ası	o Glu	3 Cys	-	Ser	Gln	Asp	Ala 40	Thr	Thr	Ile	Leu	Gly 45	Ile	Gly	Thr	144
Va]	Let 50	ı Ası	CAG Gln	Ala	Glu	Thr 55	Ala	Gly	Ala	Arg	Leu 60	Val	Val	Leu	Ala	192
ACC Thr 65	Ala	ACC Thr	CCT Pro	Pro	GGC Gly 70	AGT Ser	GTG Val	ACA Thr	ACG Thr	Pro 75	CAC	CCC Pro	AAC Asn	ATC Ile	GAG Glu 80	240
GAA Glu	GTG Val	GCC Ala	CTG Leu	CCT Pro 85	Gln	GAG Glu	GGG	GAG Glu	GTT Val 90	CCC	TTC Phe	TAC Tyr	GGC Gly	AGA Arg 95	GCC Ala	288
ATT Ile	Pro	CTI Leu	GCT Ala 100	TTT	ATA Ile	AAG Lys	GGT Gly	GGT Gly 105	AGG Arg	CAT His	CTC Leu	ATC Ile	TTC Phe 110	TGC Cys	CAT His	336
TCC Ser	AAG Lys	Lys 115	AAA Lys	TGT	GAT Asp	GAA Glu	CTC Leu 120	GCC Ala	AAG Lys	CAA Gln	CTG Leu	ACC Thr 125	AGC Ser	CTG Leu	GGC	384
GTG Val	AAC Asn 130	GCC Ala	GTG Val	GCA Ala	TAT Tyr	TAT Tyr 135	AGA Arg	GGT Gly	CTA Leu	GAC Asp	GTC Val 140	GCC Ala	GTC Val	ATC Ile	CCC Pro	432
ACA Thr 145	GCA Ala	GGA Gly	GAC Asp	GTG Val	GTC Val 150	GTG Val	TGC Cys	AGC Ser	ACC Thr	GAC Asp 155	GCG Ala	CTC Leu	ATG Met	ACG Thr	GGA Gly 160.	480
TTC Phe	ACC Thr	GGC Gly	GAC Asp	TTT Phe 165	GAT Asp	TCT Ser	GTC Val	ATA Ile	GAC Asp 170	TGC Cys	AAC Asn	TCC Ser	GCC Ala	GTC Val 175	ACT Thr	528
CAG Gln	ACG Thr	GTG Val	GAC Asp 180	Phe	AGT Ser	CTG Leu	GAT Asp	CCC Pro 185	ACT Thr	TTT Phe	ACC Thr	ATT Ile	GAG Glu 190	ACT Thr	ACC Thr	576
ACA Thr	GTG Val	CCC Pro 195	CAG Gln	GAC Asp	GCA Ala	GTG Val	TCC Ser 200	AGA Arg	AGC Ser	CAG Gln	CGT Arg	AGG Arg 205	GGC	CGC Arg	ACG Thr	624
GGG Gly	AGA Arg 210	GGT Gly	AGG Arg	CAC His	Gly	ATA Ile 215	TAC Tyr 	CGG Arg	TAT Tyr	GTC Val	TCG Ser 220	GCT Ala	GGA Gly	GAG Glu	AGA Arg	672
CCG Pro 225	TCT Ser	GAC Asp	ATG Met	Phe	GAC Asp 230	TCC Ser	GTG Val	GTG Val	Leu	TGT Cys 235	GAG Glu	TGC Cys	TAC Tyr	Asp	GCC Ala 240	720

WO 94	/2560	1													PCT/E	P94/01323
								29	0							•
GGA Gly	TGT Cys	GCG Ala	TGG Trp	TAT Tyr 245	GAT Asp	CTG Leu	ACT Thr	CCT Pro	GCC Ala 250	GAG Glu	ACT Thr	ACC Thr	GTG Val	AGG Arg 255	TTG Leu	768
				Asn	ACC Thr											816
					GTG Val											864
					AAA Lys											912
<b>Al</b> a 305	Tyr	Gln	Ala	Thr	GTC Val 310	Суз	Val	Arg	Ala	Lys 315	Ala	Pro	Pro	Pro	Ser 320	960
					AAA Lys											1008
					TTG Leu											1056
					ATC Ile											1104
					ACC Thr											1152
					TAC Tyr 390											1200
					TCT Ser											1248
GCA Ala	TTA Leu	TAC Tyr	CAG Gln 420	CAA Gln	TTT Phe	GAT Asp	GAG Glu	ATG Met 425	GAG Glu	GAG Glu	TGC Cys	TCG Ser	GCC Ala 430	TCG Ser	TTG Leu	1296
					ACA Thr											1344
					AGC Ser											1392
					GTG Val 470											1440

TAC Tyr

1443

- (2) INFORMATION FOR SEQ ID NO: 270:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 481 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 270:

Thr Ile Thr Thr Gly Ala Ser Ile Thr Tyr Ser Thr Tyr Gly Lys Phe

1 5 10 15

Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Val Ile Ile Cys
20 25 30

Asp Glu Cys His Ser Gln Asp Ala Thr Thr Ile Leu Gly Ile Gly Thr 35 40 45

Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala 50 55 60

Thr Ala Thr Pro Pro Gly Ser Val Thr Thr Pro His Pro Asn Ile Glu 65 70 75 80 Glu Val Ala Leu Pro Gln Glu Gly Glu Val Pro Phe Tyr Gly Arg Ala 85 90 95

Ile Pro Leu Ala Phe Ile Lys Gly Gly Arg His Leu Ile Phe Cys His

Ser Lys Lys Cys Asp Glu Leu Ala Lys Gln Leu Thr Ser Leu Gly 115 120 125

Val Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ala Val Ile Pro 130 135 140

Thr Ala Gly Asp Val Val Val Cys Ser Thr Asp Ala Leu Met Thr Gly
145 150 155 160

Phe Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Ser Ala Val Thr 165 170 175

Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr 180 185 190

Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr
195 200 205

Gly Arg Gly Arg His Gly Ile Tyr Arg Tyr Val Ser Ala Gly Glu Arg 210 215 220

Pro Ser Asp Met Phe Asp Ser Val Val Leu Cys Glu Cys Tyr Asp Ala

WO 94	/2560	1						29	2						PCT/EP94/01323
225					230					235					240
Gly	Cys	Ala	Trp	Tyr 245		Leu	Thr	Pro	Ala 250	Glu	Thr	Thr	Val	Arg 255	Leu
Arg	Ala	Tyr	Ile 260	Asn	Thr	Pro	Gly	Leu 265	Pro	Val	Cys	Gln	Asp 270	His	Leu
Glu	Phe	Trp 275	Glu	Gly	Val	Phe	Thr 280	Gly	Leu	Thr	Asn	Ile 285	Asp	Äla	His
Met	Leu 290	Ser	Gln	Thr	Lys	Gln 295	Gly	Gly	Glu	Asn	Phe 300	Pro	Tyr	Leu	Val '
Ala 305	Tyr	Gln	Ala	Thr	Val 310	Cys	Val	Arg	Ala	Lys 315	Ala	Pro	Pro	Pro	Ser 320
Trp	Asp	Thr	Met	Trp 325	Lys	Суз	Met	Leu	Arg 330	Leu	Lys	Pro	Thr	Leu 335	Thr
Gly	Pro	Thr	Pro 340	Leu	Leu	Tyr	Arg	Leu 345	Gly	Pro	Val	Gln	Asn 350	Glu	Ile
Thr	Leu	Thr 355	His	Pro	Ile	Thr	Lys 360	Tyr	Ile	Met	Ala	Cys 365	Met	Ser	Ala
Asp	Leu 370	Glu	Val	Ile	Thr	Ser 375	Thr	Trp	Val	Leu	Val 380	Gly	Gly	Val	Val
Ala 385	Ala	Leu	Ala	Ala	Tyr 390	Cys	Leu	Thr	Val	Gly 395	Ser	Val	Ala	Ile	Val 400
Gly				405					410				-	415	
Ala		-	420					425					430		
Pro		435					440					445			
	450					455					460				-
Pro . 465	Ala	Ala	Thr	Ser	Val 470	Trp	Asn	Lys	Ala	Glu 475	Gln	Phe	Trp	Ala	Thr 480
Tyr															

1/111
TCCACAGTCACTGAGAGCGACATCCGTACGGAGGAGCAATCTACCAAT  -AG
11a 11b 11c 11c 12a 22b 22c 23c 23c 33a 33a 33a 33a 33a 33a 33a 33a 33a 3
HCV-1 HCV-1 HCV-J BE90 2TY4 4TY4 4TY4 HC-J6 HC-J6 HC-J8 NE91 EB12 ARG6 HC-J8 NE91 NE91 NE92 NE92 NE93 NZL13 EB1 EB2 EB3 EB3 EB7 T10 BE98

_
•
7
7
(
•
- 5
·
1
2
•
ř
•
1
•
_
•
110
١,
÷

7932	TACA-AG		)	- A - GGTC	~ - ~ - \J.	~ - ~ - OLCC - ~		TAT	. «Д	A N D D	-TGN-CGA-G			-CTCACATAATGCA	7CACATATTGTATA-	-CTCACATAATGTA-T-T-	-CTCACATAATGTAT-C
	4c	4c	4c	4c	4e	4e	4 £	49	4ħ	4 i	4 j	4k	4 k	5a	<b>5</b> a	<b>5</b> a	Ба
	GB48	GB116	GB215	GB358	GB809	CAM600	CAMG22	GB549	<b>S</b> GB438	CAR4/12	CAR1/	EG-13	EG-1	BE9	) BE36	CHR18	$\overline{}$

														•														
	GTTGTGACCTCGACCCCAAGCCCGCGTGGCCATCAAGTCCCTCAC		-GCG-CA		CC-GAGG-GA-ACTACT	CT-AAGA-AACT-TAC-C-G-	5 CTCGCCAAG-GA-AACT-TAC-C	A-AACT-TAC-C	-GTAACTA	GCC-GAGG-G-TAACTTA-GCC-GAGG-G	GCCTGAGG-GAACTT-AA-A	JAGCCT-AGG-GTGACTTAC-C-	5 CCTCTT-ACC-GAGGAGACTAC-C-	-TGTCC	 	1	TGT	TGTCC	7 -CCATAGG-GA-GAAA-TGTCCG	-CATAGG-GA-GAAA-TGTCCG	TGTCC	-CATAGG-GA-GAAA-TGTCC	-GA-AAAA-	-GA-GAAT	-	₹	:-:5	
C.	א נ	21					21						14						217						_ 、	1,3	`•	
	1a	व	1c	10	2a	2b	2b	<b>2</b> p	2c	2c	2c	2c	<b>2</b> d	3a	വ	3a	3a	3a	3a	3a	3а	3a	3a	3a	3a	3a	3a	3b
•	HCV-1	BE90	2TY4	4 T Y 4	HC-16	HC-JB	NE91	EB12	s ARG6	ARG8	110 STI	<u>r</u> 1983	H NE92	五 CHR20	CHR21	CHR22	TI II	LL 26)	NE93	NZL13	EB1	EB2	EB3	EB7	BR33	BR34	BR36	T9

.

Figure 1 - Continued 2

. -

m
ರ
Ŏ
ਤ
-6
-7
ند
-
8
Con
- 1
$\dashv$
1
au
H
gure
b
·H
يعا

н	4/111
ID 7982 -CTGAG-GTGAAGGCG-TA 9 CCA-GGA-G-GTA-GAGTGA-CTAG	0
SEQ II	106 110 1110 1116 201 203 203 207 209 211 211
3b	44444444444 00000000000000000000000000
T10 BE98	GB48 GB116 GB215 GB215 GB358 GB809 GB809 GB809 GB8438 GB438 GB438 GAR4/1205 GAR1/501 GB5-19 GB BE95 GB95 GB96 CHR18

...]

.

													•										•					
,	T 8 0																			٠								
Ċ	ATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAAACTGCGG	- CT	TA	C	DDD	-C-ATC	-C-ATC	-C-ATC	-C-ATC	CC-ATC	-C-ATC	-CTC	-C-A-C	L9-222	L9-DDD	CCC-GI	CCC-AT	ICC-GI	CCC-GI	CC-GL	CCC-GI	-CCC-GI		-CCC-GI	-CCC-GI	-CCC-GI	-CCC-GL	CTCC-G
	CAATTCAAGGGG	; ; ;	A	[AA	CAGC-A	CAG	1CAGC-AA	CAGC-AA	CAGC-AA	1	I I	CAGC-AA	1	CAGC-A	AGC-A	CAGC-A	CAGC-A	CAGC-A	CAGC-A	CAGC-A	CAGC-A	CAGC-AA	CAGC-AA	CAGC-A	CAGC-A	CAGC-A	CAGC-AA	CAGT-A
	3GCCCTCTTAC	UU	BDB	GCT-G1	GCA-GTT-	GCA-GA	GCA-G-TA	GCA-GA	GCA-GA	-GCA-GA	-GCA-GA	B-	-GCA-GCTA	A-GTT-	A-GTT-	A-GTT-	A-GTT-	A-GTA-	A-GTTT	A-GTT-	CA-GTT-	CA-GTT-	A-GTT	A-GTT	A-GTT	A-GTT	A-GTTT-	-TCA-GTA
	TTTATGTTGGG	A-C	-GCCA	-GCCL	CGA-	AA-	-CCGA-	-CCAA-	-GCA	-ACA	-GCA	-ACGA-	GA-	CIGC	CIGC	CIGC	DILD	CTGCA-	CTGCA-	DLD	CIGC	DLD	CIGC	CIGC	CIGC	CTGC	CTGC	GCA-CA-
0208	AGGC	<u>-</u>	AT	AT	A-	A-	A	A	1 1 1	A-	A	A-	1 1	G	C	G	<u>ا</u> ۔ ئ	ن ن- ئ	C		C	 UD	G	 	O	C	ر- د	ر- د
	1a 1b	1p	10	10	2a	<b>2</b> p	Sp	<b>2</b> p	20	2 <sub>G</sub>	2c	2c	2d	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3b
	HCV-1 HCV-J	BE90	2TY4	4TY4	HC-J6	HC-78	NE91	<b>S</b> EB12	ARG6	ARG8	110 110	T983	H NE92	T CHR20	CHR21	F CHR22	[] 26)	<b>T7</b>	NE93	NZL13	EB1	EB2	EB3	EB7	BR33	BR34	, BR36	T9

Figure 1 - Continued 4

CGCA-C-ATCA-GTACAGT-ACTCC-G CCTGTA-GTTCAGC-AAC-AC	ACCGCTCA-GCATCAGC-AACCTGACGCTCA-GCATCAGC-AACCTGACGCTCA-GCATCAGC-AACCTGACGCTCA-GCATCAGC-AACCTGACGCCCA-GCATCAGC-AACCTTTACCGCA-GTAAGC-AACCTTTACGCTCA-GCACAGC-AACCTAACCGCTCA-GCACAGC-AACCTAACCGCTCA-GTACACCTAACCGCA-GTACACCTAACCGCCA-GTACAGC-AACCTGTACCGCCA-GCAACCTTTACCGC
3b 3c	4 4 4 4 4 4 4 4 4 4 4 4 6 6 6 6 6 6 6 6
T10 BE98	GB48 GB116 GB215 GB215 GB358 GB358 GB809 GRAMG22 GB649 GB438 GB438 GB438 GB438 GB438 GB438 GB6-13 GB6-13 GB6-13 GB95 GB95 GB96 GB18

Figure 1 - Continued 5

8082	CIAICGCAGGIGCCGCGCGCGCGCGTACIGACAACTAGCIGIGGTAACA TCATGG	) J B	))		GCA-GC-TCGGTCATGG-	ו ו לכו	1	-GC-CATTT-CTATG	3C-T	-GC-TCAGCC		-GC-TTGGC	-AC-CCAGT-CC	C-L-C	TC-TTTTATC-TCTCC	TC-TTTTATC-TCTCC	TCTCTACTTC	TC-CTCTACC-TC-T	TC-TTCTATC-TCTC	TC-TTCTATC-TCTCC	TTC-TTCTATC-TCTCC	TTC-TTC-TATC-TCTCC	TTC-TTCTATCTCC	TC-TTCTATC-TCTCC	TC-TTTCTATC-TCT-TCC	TC-CTCTATC-TCTCC	TC-TTCTATC-TC-TC	
( <del>7</del>	18 1b	1p	10	10	2a	2p	2b	2b	2c	2c	2c	2c	2d	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3a	3а	3а	3b
F 2521	HCV-J	BE90	2TY4	4TY4	HC-J6	HC-J8	NE91	EB12	S ARG6	ARG8	11 110	<b>T</b> T983	S NE92	元 CHR20	T CHR21	CHR22	TI TI	∠I 26)	NE93	NZL13	EB1	EB2	EB3	EB7	BR33	BR34	BR36	T9

Figure 1 - Continued 6

	8131 CCTC-TC-TC-T-	-AC-CCTCG	TDD-TYCT-TTCTCTCTC		DTDDTID	D)I D)I	ヴェーンボー・・・ン・	ָרָ בְּיִבְּיִבְּיִבְּיִבְּיִבְּיִבְּיִבְּיִ		-D)I -D)IQDLALB	-DDT-	1 TUC - C - C - C - C - C - C - C - C - C -	- M M M M	>I>	-		CT-C	
inued 7	8082 C-	TCC	· •	G	G	G	G	GCI	GC-AG	GCTG	-ATCTA	-AC	GB	l I	TA	TA	TI	TCT
Cont	3b	დ 4 ი	4 c	4 C	4c	<b>4</b> e	<b>4</b> e	4£	49	4h	41	4 j	4 7,	4 k	<b>5</b> a	<b>5</b> a	<b>5</b> a	<b>5</b> a
Figure 1 - Continu	T10	BE98 GB48	GB116	GB215	GB358	GB809	S CAM600	S CAMG22	GB549	₩ GB438	CAR4/1	1/501		EG-1	BE95	BE96	CHR18	CHR19

8132  CCCTCACTTGCTACATCAAGGCCCGGGCAGCCTGTCGAGCCGCAGGGCTC ATT-GACTGT-AA TATC-ATCTTGAA		-AG-G-ATAAAG-AAACG-G	-AATTA-AG-T-CG -AATTTA-AG-TGCG -AATTAG-TGCG -AATTACAG-TGCG	-AATACAA-GGCGAAGAACAATACAGTGC-AAGAACAATACAGCGAGCAATACAGCGAG	-AATACAGTGC -AATACAGTGC -AATAACAGGC -AA-AAACAGGC
	2 2 2 4 2 2 2 4 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	# # # # # # # # # # # # # # # # # # #	<b></b>	3a 3a 3b
HCV-1 HCV-J BE90 2TY4	4114 HC-J6 HC-J8 NE91 EB12	ARG6 ARG8 IIO 110 45 NE92	CHR20 CHR21 CHR21 T1 T7	NE93 NZL13 EB1 EB2 EB3	BR33 BR34 BR36 T9

,

:

	8181 - T		
	8 -GT	-GG -GG -GG -GG -GG -GG -GG -GG -GCT-G -GCT-G -GCT-A -GCT-A -GCT-A -GCT-A	, K
	H H		E
	A-CA-GT- -TACCAAT-	TATCAA TATCAATCAATCAATCAACCAACCAACCAACCAACCAACCAACCAACCAACCAACCAACCAA	 
	- G-		֖֖֖֖֖֖֖֖֡֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓
	ACT- AAA	-TCA -TCA -TCA -TCA -TCA -ACA -ACA -ACA	- 七丁丁〇 -
	<b>A</b>	DODDODDODD	1 1 1
	H H		1 1 1 1
	132 AA-AC- AAC-	-AGG -AGG -AGG -AGG -AGG -TG-AG -GG-GA -GGG -GGG -AGG -AGG	GG-
o penu	8132 -AA- -AA-	- A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - A - G - G	A-G-
- Continu	3c 3c	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	<b>5</b> a
Figure 1 -	0 863	GB48 GB116 GB215 GB358 GB809 CAM600 G22 GB549 GB438 CAR4/1205 CAR1/501 EG-13 EG-19 BE95 BE96	119
다.	T10 BE9	GB48 GB21 GB21 GB21 GB35 GB35 GB35 GB35 GB35 GB35 GB35 GB35	CHR1

---

.

Figure 1 - Continued 10

Continued 11	8231 3b A-ACCATT-CTCATGG-C	A-AA-TCCAT-AT-CTCCATG	4c AGAT-GCTT-GC		AGAC-GC-ATC-GC-TGC	AGAT-GCTT-GC-	ATGTCT	AGTCT	AT-GT-G	A-A-GTC	A-ATT	4i AT	4j A-ATGCCT	AGAT	4k A-AAT	5a -GGC-CGTTC	-GAGC-CGTTCATG-CC	LGC-C	LGC-CL
Figure 1 -	T10	Œ	GB48	GB116	GB215	GB358	<b>GB80</b>	CAM6			<b>GB43</b>	CAR4/1	T CAR1/501	EG-1	EG-	<b>BE</b> 95	BE96	_	CHR19

8271	<b>ACGCGGCGAGCCTGAGAGCC</b>	TGCAC	TD	•	A-CGA-AT	GA-A	A	: :::	TAGAA-AGC	TAGAAGC	- I - I	TAG-AGC	1	ı	•			1	-	·     
8232	AAGCGCGGGGGTCCAGGAGGA	GTAAC	AACA	GCAAC-G	GCAATAA-G	GCATAA-G	GTCAAC-G	C-C	.T-ATCG-C	-T-ATCA-T	ATCG-T	VICG-C	1	GT-ATCG-T	LD	L5	TB	TGCCG	TGCC	GTAA-
,	1a	1p	1b	2a	2b	2b	2d	3a	3a	3a	3a	3a	3а	3а	3a	3a	3a	3b	3b	30
*	HCV-1	HCV-J	BE90	HC-J6	HC-J8	NE91	NE92	S CHR20	SCHR21	CHR22	MI E	S T7	H NE93	NZL13	R BR33	m BR34	<b>©</b> BR36	T9	T10	BE38
	8232	8232 1a AAGCGCGGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC	8232 1a AAGCGCGGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC 1b GTAACTGCAC	8232 1a AAGCGCGGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC 1b GTAACTGCAC	8232  1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC  1b G-TAACTGCACT  1bAACAT  2a GCAAC-GA-CG-A-CG-A	8232  1a AAGCGCGGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC  1b G-TAACTGCACT  1bACT  2a GCAAC-GA-CG-A-CG-A  2b GCAATAA-GA-CGA-A	1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC 1b G-TAACTGCAC 1bACATAA-GA-CGA 2a GCATAA-GA-CGA-A 2b GCATAA-GA-CGA-A	1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC 1b G-TAACAGCACT 1bAACAA-CGA 2a GCAAC-GA	HCV-1  HCV-1  1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC  HCV-J  BE90  1b	HCV-1  1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC HCV-J  BE90  1b GTAACTACT  HC-J6 2a GCAAC-GA  HC-J8 2b GCAA-TAA-GA-CG-A  NE91  SD GTAA-GA-CG-A  NE92  CHR20  3a G-T-ATCG-CTAGA-AGC  CHR21  3a G-T-ATCG-CTAGAA-AGC	HCV-1  HCV-1  HCV-1  HCV-1  HCV-3  HCV-3  HCV-3  HCV-4  HCV-3  HCV-4  HCV-5  HCV-7  HC	HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-3  BE90  HC-J6  C-TAACAAC  HC-J6  C-CAAC-GA  HC-J8  BE91  SD  GCAATAA-GA-CGA-A  NE91  SD  GCAATAA-GA-CGA-A  NE92  CHR20  SA  G-TCAAC-GA-CGA-A  NE92  CHR21  SA  G-T-ATCG-CTAGA-AGC  CHR21  SA  G-T-ATCG-CTAGA-AGC  CHR22  SA  G-T-ATCG-CTAGA-AGC	HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  BE90  HC-1  BE90  HC-1  HC-1  BE90  HC-1  AGCGCGGGGGTCCCAGGAGGCCGCGCCTGAGGC  HC-1  HC-1  BE90  HC-1  AG	HCV-1  HCV-2  HCV-3  HCV-4  HCV-5  HCV-5  HCV-7  HC	HCV-1  HCV-1  HCV-2  HCV-3  HCV-4  HCV-5  HCV-5  HCV-6  HCV-7  HC	HCV-1  HCV-1  HCV-1  HCV-2  HCV-3  BE90  HC-36  LD  HC-36  LD  HC-36  HC-37  HC-36  HC	HCV-1  HCV-1  HCV-2  HCV-3  HCV-3  HCV-4  HCV-5  HCV-5  HCV-5  HCV-6  HCV-6  HCV-7  HCV-7  HCV-7  HCCV-7  HCCV	1a AAGCGCGGGGTCCAGGAGGACGCGGCGAGCCTGAGAGC 1b G-TAACAAGCAC 2a GCATAA-GA-CG-A 2b GCATAA-GA-CG-A 2b GCATAA-GA-CG-A 2d GT-ATCGC 3a G-T-ATCG-C 3a G-T-ATCG-CTAGA-AGC 3a G-T-ATCG-CTAGA-AGC	HCV-1  HCV-1  HAGCGCGGGGGTCCAGGAGGCGGCGGCGAGCCTGAGAGC  HCV-3  HC-36  HC-37  HC-36  HC-36  HC-36  HC-36  HC-36  HC-36  HC-36  HC-37  HC-	HCV-1  HC

14/111

		8232
GB48	4c	GATCAGAAA
GB116	4°C	1
GB215	4°C	- DO DO CONTRACTOR OF CONT
GB358	4c	1 1
GB809	<b>4</b> e	GTC
CAM600	4e	GT G G
G22	4£	1
GB549	49	1
GB438	4 h	<del></del>
CAR4/1205	4 i	) ひでなひ - ~ - ~ - ~ -
CAR1/501	41	
BE95	ກັດ	- CA A CA
BE96	<b>5</b> a	V V V
CHR18	5a.	 
CHR19	ת	

	2694 STVTESDIRTEEALYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGN	RA-S-PEE-HTH	LA-S		EKV-SCMF EKV-S	- E - KV - E - K - K - E - K - E - K - E - K - E - E
	2645 STVTESDIRTEEALY NS NVS		RS	QVE QVE QVE		HB
9	SEQ ID	216	146	9	218	10,12 2,4 6,8
	18 1b 1c 1c	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	2 <b>d</b>	_ w w w w w w w w w w w w w w w w w w w	# # # # # # # # # # # # #	35 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8
Figure 2	HCV-1 HCV-J BE90 2TY4 4TY4	HC-J6 HC-J8 NB91 RB12 ARG8 I10	NE92	CHR20 CHR21 CHR22 T1 T7	NE93 NZL13 EB1 EB2 EB3	EB7 BR34 BR36 T9

2645		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	VEVE-EKTA	-EVE-E-RTAMH-	VEVE-EKV-TA	-VEVE-EKTA	KVEVE-EKV-AA	-EVE-EKV-TA	-EVE-ET-KV-SAMH-	-EB-E-KV-SA	VE	N-EXDX-KV-NAMH-	E-EKV-TA	OO-XMDBBBSSMH	AHLSSSRDPCMYK-00-		OU-A-: AWDBVBVSBH
			107	109	111	113	117	202	204	115	208	210	212		162		
	<b>4</b> a	<b>4</b> a	4 <sub>C</sub>	4°C	4c	4c	<b>4</b> e	<b>4</b> e	4£	<u>4</u> g	4þ	4.	4j	<b>5</b> a	5a	<b>5</b> a	<b>5</b> a
	EG13	EG19	GB48	GB116	GB215	GB358	GB809	CAM600	CAMG22	GB549	GB438	CAR4/1205	CAR1/501	BE95	BE96	CHR18	CHR19

SUBSTITUTE SHEET (RULE 26)

2695 YRRCRASGVLTTSCGNTLTCYIKARAACRAAGLQDCTMLVCGDDLVVICE				QKI	RTPDF		RNPDFVA- 	N-RNPDF			1 1		KRSPDF	1 1 1 1 1		
18 11 10	2a 2b	ე გ გ გ გ	2 C	2d 3a	 	ช ช ก ต	ൽ ൽ ന ന	32	м к С	3а	39 3	ช ซ <b>ก</b> ต	3a	3p	3b	3c
HCV-1 HCV-J BE90 2TY4 4TY4	HC-J6 HC-J8	NE91 SB12 ARG8	110 1983	AHE NE 92 CHR 2:0	NA CHR21	JLE 2	<b>9</b> T7 NE93	NZL13	EB1 EB2	EB3	EB7	BR34	BR36	T9	T10	BE98

lqure 2 - Continued 2

Figure 2 - Continued 3

18/111

2695		γ	·	H		T			F	 · · · · · · · · · · · · · · · · · · ·		FLT		MMTi-SB-B	-HMMM		MKL	
												4 k		<b>5</b> a	<b>5</b> a	<b>5</b> a	<b>5</b> a	
	GB48	GB116	GB215	GB358	GB809	CAM600	CAMG22	GB549				H EG19				CHR18		-
									•	,01	11 U	16	υП	CC	ı (t	1UL	É 26	į

19/111

led 4	2745 SAGVQEDAASLRA TA	-Q-TEERN -Q-NEERN -Q-NEERN -Q-TEERN	-DDR-ADDRTADNR-A-GDDR-ADDR-ADDR-ADDR-ADDR-ADDR-ADDR-A
- Continued	1a 1b 1b	2a 2b 2b 2d	
Figure 2	HCV-1 HCV-J BE90	HC-J6 HC-J8 NE91 NE92	CHR20 CHR21 CHR22 T1 T7 NE93 NZL13 BR34 BR34 BR36 T9 T10

20/111

nued 5	2745 2757	-DEKRP-G-	-DEKRA-G-	-DEKRA-GV	-DEKRA-G-	-GEKRA-G-	-GEKRA-G-	-DERRA-G-	-GERA	-GERA	-I-IDKOAT	1	-Q-THE	-O-THE-N	HI	TH
- Continued		4°C	4°C	4°C	4c	<b>4</b> e	<b>4</b> e	4 £		4ħ		4 j	<b>5</b> a	5a	5a	52
- 7 einer		GB48	GB116	GB215	GB358	GB809	CAM600	G22	GB549	GB438	CAR4/1205	CAR1/501	BE95	BE96	CHR18	CHR19

	ATGAGCACGAATCCTAAAACCTCAAAAAAAAAAAAAAAA		GA-	4	A-AT		C	Ø							A-AGGA-A	51	TCGCCCACAGACGTCAAGTTCCCGGGTGGCGGTCAGATCGTTGGTGGAG	C		D					CGT	CCATTT	CCATTT	CTATACT	CTATA	CCATTTTC	
Н	AT	ı		1	1		i	1	i	i	į	į	;		i	51	TCG	<del>၂</del>	1	<u>-</u>	<u>.</u>	1	1	1 1	<u>.</u>	<del>ن</del>	5	<del>ا</del> ۔	- <del>-</del> -	<u>-</u> -2	1
SEO ID					143	٠			147	191	9		193		151																
	1a	1p	2a	<b>2</b> p	2q	3a	<u>З</u> а	3b	30	<b>4</b> C	<b>4</b> e	<b>4</b> e	4?	4?	Бa		1a	1p	2a	<b>2</b> p	2d	3a	3a	3p	30	<b>4</b> C	<b>4</b> e	<b>4</b> e	4.2	4.2	<b>5</b> a
	HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600.	GB724	EG-29	BE95		HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600	GB724	EG-29	BE95

Continued 1	a TITACITGECGCGCAGGGGCCCTPAGATTGGGTGCGCGCCAACA	1 1	- I		-W	-A	CBBA-		7-454-4-6-2-6A5		\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	)		7E-7-1-7-1-7-1-4U-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-		151	AAGACTTCCGAGCGGTCGCAACCTCGAGGTAGACGTCAGCCTATCCCAA	1 1 1 1 1		TT	A	AC	ACC-	CAG			L	DBLBB		D9L	
- Con	1a	1b	2a	2b	2d	3а	3a	3р	30	4c	<b>4</b> .e	<b>4</b> e	4.2	4.2	<b>5</b> a		1a	1p	2a	Sp	2d	സ	3a	3р	30	4c	<b>4</b> e	<b>4</b> e	4.2	4.5	Sa
Figure 3	HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600	GB724	EG-29	BE95		HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600	GB724	EG-29	BE95

																												•			
1 <u>ued</u> 2 201	Ţ		AGCTACTAATGAA-AAAC	A	A-TGAA-AA-		GAGACT		GCAATT	AAT-TAT	GCATATAG	GCAAATGT	GCTTTTTT	AAA	ACCTGA	251	CCCTCTATGGCAATGAGGGCTGCGGGTGGGCGGGATGGCTCCTGTCTCC	i	1	-CACTC	GCG	TTCAGA		ATTT	-DB		- G	1	L	•	TC-CCTAGGCT
- Continued 2	n B	1p	2a	2p	2d	3a	3a	3b	30	4°C	<b>4</b> e	4e	4.2	4?	<b>5</b> a		1a	1b	2a	2b	2d	3a	3a	3b	30	4c	4e	<b>4</b> e	4.2	45	<b>5</b> a
Figure 3	HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600	GB724	EG-29	BE95		HCV-1	HCV-J	HC-J6	HC-J8	NE92	EB1	NZL1	HCV-TR	BE98	GB358	GB809	CAM600	GB724	EG-29	BE95

iqure 3 - Continued

25/111

107	G		T4	T T	TV	I U		WD	A		F	451	CTGGCGCATGGCGTCCGGGTTCTGGAAGACGGCGTGAACTATGCAACAA	O	C	ACTTAGG			CTCAT-GGA	ACTTAC-GGA-C	ATTAC-GGA-C-TT	N-"	CACTGA
	1a	$^{1}$ p	2a	2b	2q	3a	3b	4e	<b>4</b> e	4.2	5a		1a	1p	2a	<b>2</b> p	2d	3a	3b	4e	<b>4</b> e	4.2	Sa
	HCV-1	HCV-J	HC-J6	HC-J8	NE92	NZL1	HCV-TR	. GB809	CAM600	GB724	BE95		HCV-1	HCV-J	HC-J6	HC-J8	NE92	NZL1	HCV-TR	GB809	CAM600	GB724	BE95

SUBSTITUTE SHEET (RULE 26)

4 Di i i i i i 8 8	20	5/111			
45 ACGTGCGGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCGGCGCCCCTTTTTT	TTTT	TTTTTTT	C	CTA	G
SEQ ID NO	143	13,15,17 23,25,27 19,21	89 83 85 18,18	122,169 167 171 173	2 ~ ~
11 12 12 12 12 12 12 12 12 12 12 12 12 1	2a 2b 2d	$\alpha$	4 4 4 4 0 0 0 0	4444 9944	449 4h 4i
HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HC-J6 HC-J8 HC-J8 NE92	HD10 BR33 BR36 NZL15 HCV-TR		GB809_2 CAM600 CAMG22 CAMG27	GB549 GB438 CAR4/1205

iqure 4

AA	TGG	B
L	L	

#Igure 4 - Continued
CAR4/901 4? 181
BE95 5a 143
BE100 5a 195

429 TCTTGGAGGCGCTGCCAGGGCCCTGGCGCATGGCGTCCGGGTTC		I		CAGT	~ 々 ~ 々 ひ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~		T-T-TCA-TCGA-A	-ATCAATGACC	Œ	AGA	AGGA	1	JBBBB	-GTTCA-AACTAC	)V.IIIWrWr	)WIIDWWW	3IICIAIAI	-JBDBBLL	)	-GTTCTTA		()-`)W
1 a	Ja	18 18	.1a	1b	2a	2b	2d	3a	3a	3a	3a	3b	<u>4</u> a	7 T	7 <b>4</b> 0	<u>4</u> e	4e	4£ .	4£	4g	4 h AG-A	
HCV-1 HCVEC1	HCVHCT18	HCVHCT27	HCVTH	HCV-J	HC-J6	HC-J8	NE92													GB549	GB438	
	ਜਜ	1 1 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2	122 122 122	1a 11 1a 1718 1a 1723 1a 127 1a	12 12 12 12 13	12 12 12 12 13	1a 1a 1a 1a 1b 2a 2b	1a 1a 1a 1a 1a 1b 2a 2b	1 1a CT18 1a CT23 1a CT27 1a H 1a J 1b 6 2a 6 2a 8 2b	1 1a CT18 1a CT23 1a CT27 1a Ta CT27 1a Ta	1 1a CT18 1a CT23 1a CT23 1a CT27 1a 1a 1a 1b 1b 6 2b 6 2d 8 2d 8 3a 6 CT27 3a 6 CT27 3a CT27	1a 1a 23 1a 27 1a 1b 1b 2a 2d 3a 3a	18 18 19 23 19 27 10 10 28 20 20 20 20 30 30 30 30	18 18 18 23 18 27 18 28 28 29 20 20 20 38 38 20 20 38 20 38 20 20 38 20 20 20 20 20 20 20 20 20 20 20 20 20	18 1a 1a 23 1a 1a 27 1a 23 1a 25 25 25 25 3 3 3 3 4 2 2 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	18 1a 1a 27 1a 1a 27 1a 27 1a 28 28 20 20 20 30 30 30 40 60 60 60 60 60 60 60 60 60 60 60 60 60	18 1a	118 118 118 118 118 118 118 118 118 118	118 118 129 139 139 24 4 4 6 4 f	118 118 129 138 138 338 338 440 6440 6440 6440 6440 6440 6440 6440	118 118 23 118 23 118 33 38 38 38 46 46 46 46 46 46 46 46 46 46 46 46 46	118 118 23 118 23 118 338 338 338 34 4 4 4 4 4 4 4 4 4 4 4 4

29/111

CG-GTTCATAC-GG	CGGTCATCACTGACTG
5.4	5 S A
CAR4/901	BE95 BE100

Figure 4 : Continued 3

30/111

Figure 4 : Continued 4	1a B	HCVHCT23 1aC-T	HCV-J 1bTGC	HC-J6 2aGTT-TT-ACCT HC-J8 2bGA-ATCTT-ACT NE92 2dGA-AT-GC	aGA-AT-TCTT-GCC	3aGA-AT-TCTT-GCCC	TR 3b	4.	ਰਾ ਰਾ	CC	4	CAMG27 4fGA-A	•
------------------------	------	----------------	-------------	--	-----------------	-------------------	-------	----	-------	----	---	---------------	---

SUBSTITUTE SHEET (RULE 26)

GA-CTT	GA-TCT	GACTT-AC	GIIIIII
<b>4</b> i	4?	5a	5a
CAR4/1205	AR	E30	BE100

Figure 4 - Continued 5

: Continued 6

Figure 4

32/111

529 TTCCTTCTGGCCCTGCTCTTGCTTGACTGTGCCCGCTTCGGCCTACCATC	T-G	TTTA-TCCATAAG-TAGTCTAGTTTA-TCCATAAG-T-GTCTAGTTTT
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	22 24 24 24	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HC-J6 HC-J8 NE92 NE92	HD10 HBR33 HR36 HZL15 HCV - TR

:

\_.

33/111

578	TTGTCCTGCTAGTT-C ATGC-C
-CCT	TAT
4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	5 5 5 8 8
GB809_4 Z4 Z1 Z1 GB116 GB215 GB358 Z6 Z7 DK13 GB809 Z2 CAM600 G22 G22 G27 G22 G27 G22 G27 G27 G27 G27	BE95 BE100 SA4

34/111

inued 8	628 AGTGCGCAACTCCACGGGGCTTTACCACGTCACCAATGATTGCCCTAACTTTCTTTTTT	AAGATGTACCGGCATGGCCA-CTG CA-GATT-GTTCTAGCTCTT-AA GCAAGGAGGC-ACTCCATGCCGCT-C GCAAGAGCA-CTCATG-ACAGA	GTGGTA-GT-TCCTGT-C-TCCTT-CTA GTGGTA-GT-TCTGT-C-TCCTT-CTA GTGGTA-GT-TCTGT-C-TCCTT-CTA GTGGTA-GT-TCCGT-C-TCTT-CTA GTGGTA-GT-TCCGT-C-TCTT-CTA
Conti	11 11 12 12 12 12 12 12 12 12 12 12 12 1	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
Figure 4 - Continued	HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HS STUTES HE SB3 NE 92	HD10 BR33 BR36 NZL15 HCV-TR

969	7GT-	ַ ט וייי פ	1 1 1 1	E-	1 ! !	- 1	ر ان ان ان	1	1	ר - בי בי בי	<del>-</del>	 	!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!		1		B	A	A	A
		 	! ! ! ! !		·			ן ה	ــــــــــــــــــــــــــــــــــــــ		ן כ		-TC	1 1 1		1		1 1 1 1 1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	T	- 1	<u>L</u> -	1		T	ı	- 1	 	T	- <b>T</b> -	 	- L L-	L-	ı	-TT-	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-TTT-	- T T T -	- L - L L -
	TTCA-C-	- 1	- BD	1	Ĭ	TCA-C	TCG-	rgg-	TTG-	<del>5</del> 2	1 1	]		I	1 1	A	TCA-C-	T-TA	T-TA-C-	I-TG
٠	CGTG-	CGLG-L	7GTG-T	rg	DLJ		L	TG	AG-	TT		T-A1	1	GAT-	GTG-AT	TG-	GTGT-	ATG	ATG1	AG1
579	a CTAC	a CTA	b CTAC	c CTAT	c CTAT	CCTAT	CTAT	CTAT-A	d CTAT	CTA	CTA	TTA	TTAT	y CTAC	CTAC		CTAC	L CIAC	CTAC	CTAC
	4	45	•	6 40		7	40	40	7	. 7	10 7	4 f	4 f	4	4	205 4	901 4?	<b>5</b> a	58	<b>5</b> a
	GB809	24					92		DK1		CAM				<b>GB43</b>		CAR4/	<b>BE95</b>	E1	SA4

629	AGGCGGCCGATGCCATCCTGCACACTCCGGGGTG					D V -	ATCACC-GGC-ACTCCAG-CTGTGACT-C-GC-ACTCCAG	A	٠ د د	TGTC	)	GC	1			IGI
	1 1 a	n Ta	1a	la	1a	1b	2a	<b>5</b> p	2c	2d		3a	3a	3a	3a	3b
	HCV-1 HCVEC1	HCVHCT18	HCVHCT23	HCVHCT27	HCVTH	HCV-J		12 HC-J8	383 <b>Ú</b> T	ME92	SHE	HD10	39 BR33	F BR36	5 NZL15	HCV-TR

629 -CCG-ACTAA-T-A-C-CCATATTTG -CAC-TAT-A-CCAATTG	GA	C-A-C-CCAA-	CAA-C-AGC-CCAACTCAT CATC-AAC-CCAGT-ACTCA	TC-AAC-CCAACTC	CTC		CAA-C-AAACAT-ACTC	C-TT	C-TTA-AGCCATTCTAA-	A-CCATATCTA	-CAACTAC	C-AGA-CCATCT-	ATC-CCAATTAA	-CTA-ATA-CCTGAG-AT	A	TTG-A-
44 A	4 4 5	4c	4, 4, D D	4c	4q	<b>4</b> e	<b>4</b> e	4£	4£	<b>4</b> g	4h	41	4.5	<b>5</b> a	<b>5</b> a	<b>5</b> a
GB809_4. Z4	Z1 GB116	GB215	68358 . Z6	22	S DK13	GB809	CAM600	<b>™</b> G22	E G27	王 GB549	<b>GB43</b>	CAR4/12	E CAR4/901	BE9	团	SA4

i

- Continued 11

Figure 4

.

38/111

728   GTCCCTTGCGTTCGTGAGGCCAACGCCTCGAGGTGTTGGGTGGCGATGAC	GAGAAA-TGTA-ATCCA-ACG-CT- AT-AGAATAATGG-AT-CATCA-ACAAG-A T-AGACC-CTTC-ACG-TG- T-AGGAGAATACC-CA-ACG-TT-	ATAGCTTA-ATGCCACCC-AG ATC-AGCTA-GT-CACACCC-AG-A A-ATC-AGCTA-AC-CACCC-AG ATC-AGCTA-AT-CACCC-AG
122 122 122 122 122 123 123 123 123 123	20 20 20 20 20	33 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HC-J6 HC-J8 S83 NE92	HD10 BR33 BR36 NZL15 HCV-TR

nued 13	AC
Contin	фффффффффффффф БСС В в в р г г г г г г г г г г г г г г г г г
Figure 4 -	GB809_4 Z4 Z1 GB116 GB215 GB215 GB358 Z6 Z7 DK13 GB809_2 GCAM600 G27 G22 G22 GB549

40/111

729 CCCTACGGTGGCCACCAGGGATGGCAAACTCCCCGCGACGCAGCTTCGACC	AG-ATGTGCA-C-GCC-GGCGCT-ACA-GGCT-AGA AC-ACTGTG-AAC-CCGGTGCG-T-A-TCGTAGCGAC-ATC-CTATC-ACCTGGCGCT-T-A-T-A-GGCGG GC-ATA-ATGTGCC-ACCTGGTGCG-TTA-C-A-GGCGGA AAAGTT-C-T-GG-GCAAA-CG-TTC-A-ACA AAAGTT-C-T-GG-GCAAA-CG-TTC-A-ACA AAAGTT-C-T-GG-GCAAA-CG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA AAAGTT-C-T-GG-GCAA-TA-TG-TTC-A-ACA
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	22 20 20 30 30 30 30 30 30 30 30 30 30 30 30 30
HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HC-J6 HC-J8 S83 NE92 HD10 BR36 BR36 HCV-TR

C	ρ / ,												-							
729	TGGTATCCATGG-CGCTGCTCGA-TCCT-C	GCTTGA -	-GTTAGA-TCCA-G-	CCGG-GCCTT-C-TTGGTGCTGCTAGAATCC-	CCGG-GCCTT-CAT-GGTGCTA-TTGAATCCT-C-	CAT-GGCGCTGCTTGAATCCC-	CCGGTGTCTTAT-GGTGCTGCTTGACTCCC-	CCCGG-GCCTTAT-GGTGCAGCTTGAATCCA-C-	-CTGTGCT	GT-GCCTT-C-T-GGTGCT	-AA	CCTTGGCGCT	TG-GCCAC-CATTGGCGCT	-TTGCCCTTTGGCGCGGCTCGAATCCA-G-	-AGT-CCT-CCT-GGGGCT	GGCCAC-CCTACGTGCTGCTTTTCCT-A	CCT-GGGGCTGCTTTCA-	ACT-AGCC-AGCCT-GG-GCAGT-AG-T-CTGA	T-CC	AG-T-GA
	<b>4</b> a	<b>4</b> a	<b>4</b> b	4c	4°C	4c	4c	4c	<b>4</b> d	<b>4</b> e	<b>4</b> e	4 £	4 £	<b>4</b> g	4h	<u>4</u> ;	4?		<b>5</b> a	
	GB809 4	Z4	Z1	GB116	GB215	GB358	<b>9</b> Z	12	Ω	O	U	_	<b>G</b> 2	GB54	GB438	CAR4/	3 CAR4/901	BE95	国	SA4
								SI	UBS	III	UTI	: 5	HEE	T.(	KUL	Ł Z	(6)			

42/111

779	ACATCGATCTGCTTGTCGGGAGCGCCACCCTCTGTTCGGCCCTCTA				I		-CGTCTGCGTG-T	CGTCAGGAT-TCGCCTT-	CAGCAA-CAAT-GCATGGCCT-GT	CATTTCTT-T-T-TTTTTT	CGTTACCA-CA-T-CATCTGT-TCTG		-GTG-ACAT-GGCGCGGA-GCTT	TG-GCT-AACGCGGA-GCTG-T	TG-GCAT-AGCGCGGA-GCTG	TG-GCAT-AACGCGGA-GCTG	CCTG-GAGACGCACGACAAGGGG
	1a	1a	1a	1a	1a	1a	1p	2a	<b>2</b> p	2c	2d	ı	3a	3a	3a	3a	3p
	HCV-1	HCVEC1	HCVHCT18	HCVHCT23	HCVHCT27	HCVTH	HCV-J				NE92					NZL15	
								SUE	ST	MU	TE S	HE	ET	(Rl	JLE	26	)

	-GTG-GCAA-GA-TGCGG-G-G	-TG-GCT-AA-GACGCGTT-G	-CA-GGTGCGTTA-GA-GTT-	-TG-GA-G-BTTG-TRB-BB-B	CAA-GGGGTTTTCCCGTTT					JJB-5BBBBBB-	IG-GCA-GA-TGCTA-GC		VUUVVVVVVVVVV-	G-GCT-AA-GGTGCGG	-TG-GCA-GGGGD-ACD-B-	-ТG-GСAA-G	.TG-GTA-GGTGCATT		TCTACA-CGAG-GTGCC-	-GAG-GTGCC-	-71
7.2	ros ros	æ	ڡ	Ð	נ	4c	73	<b>r</b> )	~	a	a.			-	4h AG-				K I	1	
	9_4			91	15			27		GB809 2	$CAM60\overline{0}$	G22	G27	GB549	GB438	CAR4/1205	CAR4/901	; ;		五100	SA4

44/111

878 GTGGGGACCTATGCGGGTCTGTCTTTCTTGTCGGCCAACTGTTCACCTT	T CA T T T T T T T T T T T T		TTA-GTG-CCGAGCCGTTA-GTG-CCCGAGCCGTTA-GTGCCGAGCCGTTA-GTG
д н н н н н	1a 1a 1b	22 20 20 20	6 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8
HCV-1 HCVEC1 HCVHCT18	HCVHCT23 HCVHCT27 HCVTH HCV-J	HC-J6 HC-J8 SB3 NE92	HD10 HBR33 BR36 HZL15 HCV-TR

\_ :

.

!

--|

																	•				
	TACTAGGCTCAGGGA	-CGA-GC-				77-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-			-9-IY99- -9-IY9919-9Y9	-:	ーー・・ジー・ジー・ひー・ひー・マールンジントー・・・				-WDD- -RDDRD-D-LD-LD-DD	99	-D)		AGCGTG-AC-ACT-GAA	- A	G-AGT-GA
,	<b>4</b> a	<b>4</b> a	4p	4c	4c	4 C	4 c	4 C	4 d	4 e	<b>4</b> e	4£	4 £	49	4 h	41	4.2	:	<b>5</b> a	<b>5</b> a	5a
	GB809_4	24	<u>Z</u> 1	GB116	GB215	GB358	26	- 7Z 27	SE DK13	∃ GB809 2	CAM600	⊈ G22	H G27	GB54	E GB438	CAR4/12	CAR4/901		BE95	E1	SA4

ignire 4 - Continued

,

46/111

GACGACGCA		-ATC-CGT-TG	GACAATTTGTAC	AAACAA	GCAATTAA-TTTGTCG-ACCTCAC-	-AGATC-TTCAAGTCGACCTCAC-GC-	-AGAC-CTCAAGTCGACCTCGC-G-C-	-AGATC-TTCAAGTCGACCTCGC-GC-	-AGATC-ATCAAGTCGACCTCGC-G-C-	-AGATC-CACCGTGACG
1 1 1 2 c c	7 8 8 8 1 1 1 1 1	1b	22 7	20 20	2d	3а	3a	3a	3a	3p
HCV-1 HCVEC1 HCVHCT18	HCVHCT23 HCVHCT27 HCVTH	_	ILSBN	383 383 383	NE92	18) HD10			_	HCV-TR

j

.. :

\_#.

	928	1	a			_		_														
	σ					ו ו ו ו כ		1	5)				ן ן	ָל וּ			]		<b>t</b>	αリー-L	L	  -     
		-CG-AT-	י י טיי מיי	יליים - לייים - לייים	) 	ני יי יי		)	, <del>[</del>		ברים - ברים ברים ברים ברים	コープマーヴー	ָרָי   	- טיייטיי	C C	ן די ו		CIG-		-GTGAAC	i	 
<u>ued</u> 21	879	-CAGGC-T	TCGGGC-T	-CGAGC-CG	1	- [	GC-	i	GC-	1	-GC-A	1	C-C-T	C-C-IG	-ე-ეე-	- D	Ą-	G		TAGGTC-C-AGGCT	PAGGTC-C-AGTGCT	TAGGTC-C-AGACT
- Continu		4a	<b>4</b> a	4p	4c	4c	4c	4c	4c	4d	4e	4e	4 £	4£	·4q	4 <u>h</u>	4 i	4.5			5a	
Figure 4 -		$GB809_4$	24	<b>Z</b> 1	GB116	GB215	GB358	92			GB809	CAM600	<b>\$</b> 625			GB438	12	© CAR4/901		BE95	BE100	SA4

48/111

929 CCGGCCATATAACGGGTCACCGCATGGCA CG	-TTACCCTA	-AC-TT-AAT -AC-TT-AATAT -AC-TT-AATAT -AC-TT-AATAT
11 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2a 2c 2d	
HCV-1 HCVHCT18 HCVHCT23 HCVHCT27 HCVTH	HC-J6 HC-J6 HC-J8 S83 NE92	HD10 BR33 BR36 NZL15 HCV-TR

49/111

Continued 23	929	.TCCCA-GC		TCG-CTCA-G	CG-TCA-G	GCLCB	CG-TCA-G	DDB-	GCG-TACA-A	ACAA-A	-GTT-	CL	CTA-	)	CTA-A	GGG	GCC	C	GTG-TCCG	1 1	יייי ביייי ביייי ביייי ביייי ביייי ביייי ביייי ביייי ביייי בייייי ביייי בייייי בייייי בייייי בייייי בייייי בייי
Cont		<b>4</b> a	<b>4</b> a		4°		4 C	4c	4c	4q	<b>4</b> e	<b>4</b> e	4£		49	4h	41	4.2	<b>5</b> a	<b>5</b> a	L E
Figure 4 -		GB809 4	Z4	21	GB116	GB215	GB358	<b>9</b> Z	27	DK13 :	GB809 2	CAM600	G22	G27	GB549	GB438	CAR4/1205	CAR4/901		BE100	SA4

		50/111	
1 MSTNPKPQKKNKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATR R-T		R-TC LRQTLN	RR-T
SEQ 1D	144	148	192 164 166 194 152
1a 15	2a 2b 2d	3a 3b 3c	4c 4c 47 5a 5a
HCV1 HCVJ	HCJ6 HCJ8 NE92	EB1 NZL1 HCV-TR BE98	GB358 GB809 CAM600 GB724 EG-29 BE95

7
밁
in
lit out
ပ
2
<u>r</u>
igu
u.

		51	1/111		
	KTSERSQPRGRRQPIPKAR RPEGRTWAQ PGYPWPLYGNEGCGWAGWLLSP				AL
V-core	RPEGRTWAQ	DST-KS-GK DST-KS-GK DT-KS-GK	-SS -SS -TS	-SSSSSSS	Q-TS-G-
	KTSERSOPRGRROPIPKAR	- Q	KQ-HL		
	1a 1b	2a 2b 2d	33 35 30 30	45 45 45 45	5а
	HCV1 HCVJ	HCJ6 HCJ8 NE92	EB1 NZL1 HCV-TR BE98	GB358 GB809 CAM600 GB724 EG-29	BE95

52/111

	126 RGSRPSWGPTDPRRRSRNLGKVIDTL		XNXX-	
. Con	1a 1b 2a 2b 2d	3a 3b 3c	4e 4e 45	ת
Figure 5 - Continued 2	HCV1 HCVJ HCJ6 HÇJ8 NE92	NZL1 HCV-TR BE98	GB809 CAM600 GB724	BE95

53/111

		176
HCV-1 HCVEC1	<u>6</u> 6	TCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSFSI
HCVHCT18	<u>a</u> <u>a</u>	
HCVHCT27	<u>, a</u>	
HCVTH HCV-J	1 a	
HC-J6	2a	
HC-J8 NE92	97 77	
HD 10	3a	1
BR33	3a 3	
BA30 NZL1	7 a	1 1 1
HCV-TR	3b	

Figure 5 · Continued 4

54/111

127					1				!	1	1	1		**************************************	
	<b>4</b> a	4c	4c	4c	<b>4e</b>	4е	44	44	<b>4</b> 9	44	4 i	<b>ċ</b> 5	i L	ו ס	5a
	GB809 4	GB116 <sup>-</sup>	GB215	<b>GB358</b>	GB809 2	CAM600	CAMG22	CAMG27	<b>GB549</b>	GB438	CAR4/1205	CAR4/901	o U	0673	BE100

55/111

	226		•	•
		PGC		1 1 1 1 1
	· 72	TNDCPNSSI VYEAADAILHT PGC	TWALAA-VV TWALTVL -WALEG-V	D-VA
		TNDCPNSSI	S-N	
	E1 v1	YQVRNSTGLYHVS HS	I-T-V AE-K-ISTG-M- VV VEISSS-YA VE-KDTGDS-MP IV-G LK-TSSS-M-	
inued 5	177	FLLALLSCLTVPASA YQVRNSTGLYHVS HS	9-AI	FIHAS LEWTSVLFIHAS LEWTSVLFIHAS LEWTSVLFIHAS LEWTSVL
- Conti		6 6 6 6 6 C	28 26 24	33a 33a 35
Figure 5 - Cont		HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVHCT27 HCVTH	HC-J6 HC-J8 S83 NE92	HD10 BR33 BR36 NZL1 HCV-TR

56/111

226			1 1
V2	TDHH	DNLA	-LDAML
	A A A		1 8 8 8 1 1 2
>	EHY AS - 1 1 EHY AS - 1 1 VHY AS - V 1 VHY AS - V 1 IHY AS - V 1 IHY AS - V 1 VNY AS - I I VHYH-TS - I I VHYH-TS - I I QHY IS - I 1 GHY AS - I IHY AS DG - YI	VPYAS-I VPYAS-I VPYAS-V	LTYGSL
177	S - T	>>> 	
	44 44 44 44 45 45 45 45 45 45 45 45 45 4	5 5 8 8	<b>6</b> a
	GB809_4 24 21 21 GB116 GB215 GB258 26 27 DK13 GB809_2 CAM600 CAMG22 CAMG27 GB549 GB549 GB438 CAR4/1205	BE95 BE100 SA4	HK2

57/111

276 PUTATIVE	LRRHID LLVGSATLCSALY	MI-MAA II-MV	MAM AM AM MARQ
74	TRDGKLPATQ	VQQPGALTQGT VKHRGALTRST-V- ISQPGALTKGA VSQPGALTKGT	-QDT-ATPV V-YVGATTAS IVQDT-TTPV V-YVGATTAS I-S-VQDT-TTPV VKYVGATTAS I-S-VQDT-TTPV V-YVGATTAS I-S-VTTQ-STTV ST V-TLGVTTAS I-T-V-
	1VAM TPTVA	IPV S-N IQVN -PV A-NL- IPV S-NI-	ATPV TTPV TTPV STTV ST
V3	VREGNASRCWVAM TPTVA -HVVD-VVKPV A	EKVTIPV S-N ENDNGTLHIQVN E-TA-VPV A-NL- EEKIIPV S-NI-	-QDT-ATPV -QDT-TTPV -QDT-TTPV -QDT-TTPV
227	VPC	1 1 1 1	1 1 1 1 1
	<u> </u>	2a 2b 2c 2d	3a 3a 3b
	HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVTH HCVTH	HC-J6 HC-J8 S83 NE92	HD10 BR33 BR36 NZL1 HCV-TR

58/111

	276 PUTATIVE	11122222	-MAM	Y-A-G-A YG-A Y-A-G-A
		##E:#:	X X X X X X X X X X X X X X X X X X X	AV- AV- AV- FV-
	77	AVSMDA-LES VAHPGA-LES APYPNA-LES APYIGA-LES APYIGA-LES APYIGA-LES VSYIGA-LES APYIGA-LES SPYVGA-LES	SPYAGA-LEP APYLGA-LES APHIGA-LES APYVGA-LES VPYLGA-L-S APHLRA-LSS	APSLGAVTAP APSFGAVTAP APNLGAVTAP IPNASTG
				S
	Λ3	AVTPVTE-TPLVQLVQLVQLVQLVQ		-MTVQI KD-VQI QD-V-KQI VDDR-TH-V
nued 8	227		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
· Continued		40 40 40 40 40 40 40 40 40 40 40 40 40 4	44 44 44 44 45 45	5а 5а 6а
Figure 5 -		GB809_4 Z4 Z1 GB116 GB215 GB358 Z6 Z7 DK13 GB809_2	CAMG22 CAMG27 CAMG27 GB549 GB438 CAR4/1205	BE95 BE100 SA4 HK2

59/111

	319	SPRRHWTTQG CNCSIYPGHITGHRMA		RQ-V-TLLS RQ-V-TLS RQ-V-TLS RT-V-TLS
	. ^2	SPRRHWTTQG	QHFV-D QNFE QH-TFV-E QH-KFV-D	RQ-V-T RQ-V-T RQ-V-T RT-V-T
inued 9	277 TRANSMEMBRANE DOMAIN	VGDLCGSVFLVGQLFTF	G-M-AA-M-IVQHFV-DVA-MILS-A-MVQNFE IA-M-AA-VVVVQH-TFV-E IA-M-AS-V-IIQH-KFV-D	MA
- Cont		<u>a a a a a a</u>	2a 2b 2c 2d	3a 3a 3a 3b
Figure 5 - Continued 9		HCV-1 HCVEC1 HCVHCT18 HCVHCT23 HCVHCT27 HCVTH	HC-J6 HC-J8 S83 NE92	HD10 BR33 BR36 NZL1 HCV-TR

60/111

	319	T	A - V	
	75		QD QD QD RLE RLE RI-ED QD	RQ-A-V-N RQ-A-V-D RQ-T-V-D QV-D
	,	2 2 2 2 2		<b>&gt;&gt;&gt;</b> ;
nued 10	277 TRANSMEMBRANE DOMAIN	I GA MMI I GA MMI I G M I G M	I G M-  I G I M-  I	AALM- AALM- AAM- ILA
Conti		6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	4c 4c 4c 4d 4d 47 47 40 40 40 40 40 40 40 40 40 40 40 40 40	6 575 8 8 8 8
Figure 5 - Continued 10		GB809_4 24 21 GB116 GB215 GB358	26 27 27 0K13 GB809_2 CAM600 CAMG22 CAMG27 GB549 GB549 GB438 CAR4/1205	BE95 BE100 SA4 HK2

4648 GTGTGCCAGGACCATCTTGAATTTTGGGAGGGCGTCTTTACAGGCCTCACTC	AG	-ACA	7997	0527	CATATAGATGCCCACTTTCTATCCCAGACAAGCAGAGTGGGGAGAACCTT C	CA		CAGACTCT-C	ACAGACTCT-C	ACAGACTCT-C	↑ 4731
HCV-1 HCV-J	HC-J6 HC-J8	HCC153 EB1	EB2 EB6		TUTE:	왕 왕 왕	M HCC (53		€ EB2 FB6	E87	

Figure

62/111

4751 CCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCTAGGGCTCAAGCCCCC	4801  TCCCCCATCGTGGGACCAGATGTGGAAGTGTTTGATTCGCCTCAAGCCCA  AT
HCV-1	HCV-1
HCV-J	HCV-J
HC-J6	HC-J6
HC-J8	HC-J8
HCC153	HCC153
EB1	EB1
EB2	EB2
EB6	EB6

63/111

	4900 3GGCGCTGTTCAGAT A-A-CA T-C-GACC GCC-A -C-A -C-A -C-A -C-A -C-A -C-A -C-A -C-A -C-A -C-A -C-A
	4850 CCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTCAGAAT -AGTGCCCCCCAAGTGCCCCTCGCTTGACCAGACTGTTGCT
continued 2	SEQ ID NO 29 31 35 37 39
Figure 6 - continued 2	HCV-1 HCV-J HC-J6 HC-J8 HCC(53 HD10-1-25 HD10-

. .

..

.

64/111

65/111

5040	GTCCTGGCTGCTTTGGCCGCGTATTGCCTGTCAACAGACTGCGTG			T. A			164 - AGCGCC-AGCTGTCTTT		165 -AGGTCTTT	5041	TAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATACTTG		TGCA-CC-CT-GCA-G-TAA-CA-CGAG-C-TCG-TG	TCCA-TC-CC-ACA-CAAT-ATCG-GTTTG-GGCC	5CTCATAAGCGGGC	AC	164	166	
	HCV-1	HCV-J	HC-16	HC-18	HD10-1-25	HD10-1-3	BR36-20-1	BR36-20-1	BR36-20-1		HCV-1	HCV-J	HC-J6	HC-J8	HD 10-1-25	HD10-1-3	BR36-20-16	BR36-20-16	PP74-20-14

5091 CAGGGAAGTCCTCTACCGAGAGTTCGATGGAAGAGAGGTGCTCTCAGC	-A	AAT-ATGAG-CCTAG-CTCCA	AGGT-GT-A-CA	AGGT-GT-A-CAGGG-		AAGGT-GT-A-C-A-AAAG			5141	ACTTACCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAG	C-CT	GAGCGG-TCTTAG-GCA-CG-A-AAT-C-GTCC	-AGCCG-CCTTGCA-CG-A-GGAT-CATCT	C-GCCA	C-GCCAACTCA-G-AA-AC-CG	CTGCCATACTCA-G-AA-ATC-CGGA	CTGCCATACTCA-GA-ATC-CG-A	CTGCCATACTCA-G-AA-ATC-CG-A
HCV-1	HC-16	HC-J8	HD10-1-25	HD10-1-3	BR36-20-164	g BR36-20-166	्ष्यु BR36-20-165	IUTE :	SHEE	HCV-1	HCV~J	_		HD10-1-25	HD10-1-3	BR36-20-164	BR36-20-166	BR36-20-165

	5191
HCV-1	AAGGCCCTCGGCCTCCTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGC
HCV-J	GAT-GACAAAGAGC-GCT
HC-J6	ATAAT-ATCAATAAAATC-A-ACACA
HC-J8	ATA-AAACAGCA-AA-GTC-A-AC-ACA
HD 10-1-25	AATTAGCGACAAAACACTCT-A
HD10-1-3	AATTAGCGACAAAACACTCT-A
BR36-20-164	A-TTAT-GCGACAAAACACTCT-A
BR36-20-166	A-TTAT-GCGACAAAACACTCT-A
BR36-20-165	A-TTAT-GCGACAAAACACTCT-A
	5241
HCV-1	GCTGTCCAGACCAACTGGCAAAACTCGAGACCTTCTGGGCGAAG
HCV-J	TC-1GGTG-GCCTGGAA
HC-J6	ACG-TTCTCCGG-ACAA
HC-J8	GAA-AT-ATCACCGTACAAT
HD10-1-25	GC-TAA-AGCTTGTACAC
HD10-1-3	GC-TAA-AGCTT
BR36-20-164	GCATAAACT
BR36-20-166	GCATAAACT
BR36-20-165	GCATAAACTGTGTCATA

Figure 6 - Continued 6

Figure 6 · continued 7

HCV-1

HCV-J

HC-J6

HC-J8

HC-J8

HD10-1-25

HD10-1-25

HD10-1-3

BR36-20-164

---

5	۵	1	1	1	1
v	7	∕.	1	1	1

09/:111	
1330 G - - -	1380 YGKAI 
1290 1300 1310 1320 1. ITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGG	1340 1350 1360 1370 1 TVLDQAETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAI
1290 1300 1310 1320 ITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIG	1360 PHPNIEEVA
13 GGCSGGAYD A	1350 ATPPGSVTV I T
1300 STYGKFLADC C	1340 AETAGARLVVLAT
1290 ITTGSP ITYST G VDS	TVLDQAETA
0	
SEQ 1D 1	·
1a 2b 2b 5a	1a 2b 2b 5a
SIBSTITUTE SHEET  HENS BLUTTESHEET  SHEET	HCV-1 HCV-1 HC-16 BE95

.

-1

. ...

70/111

	1420 1430 GLDVSVIPTSG	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-0	-0	A	1470 1480	FTIETITLPOD	<u>-</u>	T-0-L	\-\-\-\-\	\-L
	1410 EVALGINAVAYYR	-TGL	-RGM-L	A-RGM-V	K0-TSV	1460	:VTQTVDFSLDPT		V-D-1	I-S-VA	SA
,	1400 KKKCDELAAKI		A-RGM-L	1 1	K0-	1450	DFDSVIDCNTC		ηΛ	1	dS
1 1 1 1 1	1390 1400 1410 1420 14 PLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG	-I-ATGL	SY	AF	AF	1440	DVVVVATDALMTGYTGDFDSVIDCNTCVTQTVDFSLDPTFTIETITLPQD				CSF
		<b>1</b> b	. 2a	<b>5</b> P	<b>5</b> a		<u>1</u>	<del>1</del> b	2a	Sp Sp	5a
	HCV-1	HCV-J				e sheet (		L-VOH E		HC-18	BE95

	1490 1500 1510 1520 1530 AVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCAWYELA		1540 1550 1560 1570 1580 TPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSG	- Y		-9WN	-0
nued 2			SEQ ID NO				223
- Conti	1 <del>1 a</del>	2 <del>5</del> 5a		16 2a	Sp	5a	<b>3</b> a
Figure 7 - Continued	HCV-1 HCV-J	SIBELLITIE SI		L-V-1 HCV-1		BE95	BR36
		CODOTTIOLE O	irri (u	ULL 20	7		

72/111

Figure 7 - Continued 3	ENLPYLVA	SVTKKX	. –	1640 1650 1660 1670 1680 VQNEITLTHPVTKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIA
· Cont	<u>1</u>	2a 2	5a 3a	1a 1b 2a 5a 3a
Figure 7	HCV-1	HC- J6 HC- J8 HC- J8	BE95 BR36	RR36 STAILLISERIS ALCV-1 RC-16 RR36 BE95

Figure 7 - Continued 4

		7	/3/111	
1730		~		
		LAEQFKQ  IML-S MML-S I-HE I-GE		
1720	NS4-5	SQHLPYIEQGMM ASQ ASRAALE-QR ASKAALE-QR AAAQV		
1710	SN		90	4+++++++++++++++++++++++++++++++++++++
		MEEC	1760	
1700		VGRVV LSGKPAIIPDREVLYREFDE MEECIIRVQ ILH VNQRAVVAK-IEA ILH -NDRVVVAK-IEAHIE -GVKQQY	1750	ALGLLQTASRQA EVIAPAVQTNWQKLETFWAKHTKAAV-ESK-RAV IQQK QD-QAS-P-V-Q IQQ-T QD-QI-SS-PQ VR-IQ-Q AE-I-TAH VR-IS-TGQKTLKATSV-N-A-QXTY
1690	NS4-1	LSGKPAIIPDREVLYREFDERVQ VNQRAVVAKEANDRVVVAKQQYGVKQQY	·	EVIAPA -AAV QD-Q QD-Q AE-I
		LSGKPA R VNGRAV -G	1740	TK TK TGGK T
		VIVGRVV   C-111   S-1LH   S-1HIE   A11   C-1HIE   C-1HIE   C-1HIE   C-1-HIE   C-	NS4-7	ALGLLQTASRQA
	·	1a 1b 2a 3a 5a		18 28 38 58
		HCV-1 HCV-J HC-J6 HC-J8 BR36 BE95		HCV-1 HCV-J HC-J6 HC-J8 BR36 BE95

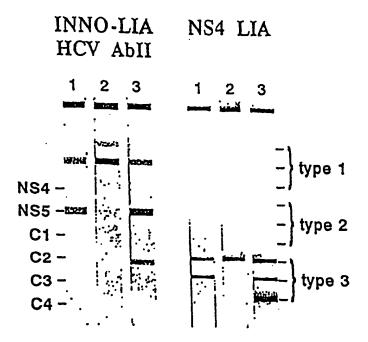


Figure 8

75/111

ATGAGCACGAATCCTAAACCTCAAAGAAAACCAAAAGAAACACCAACCG	100 TCGCCCACAGGACGTCAAGTTCCCGGGCGGTGGTCAGATCGTTGGCGGAG	
SEQ ID NO 49 51 41 43 53		
PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1		PC-4-1 PC-2-6 PC C/E1

Figure 9

76/111

Figure 9 . Continued 1	150 TITACTIGTIGCCGCGCGCGCCCTAGGATGGGTGTGCGCGCGCGACTCGG	AAGACTTCGGAACGGTCGCAACCCCGTGGACGGCGTCAGCCTATTCCCAA
Figure 9	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1
<b>11-</b>		

77/111

Figure 9 · Continued 2	201 GGCGCCCACGGGCCGGTCCTGGGGTCAACCCGGGTACCCTTGGC	251 CCCTTTACGCCAATGAGGGCCTCGGGTGGGCAGGGTGGCTGCTCTCCCCT
Figure 9	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1

78/111

Figure 9 - Continued 3	350 CGAGGCTCTCGGCCTAATTGGGGCCCCCAATGACCCCCGGCGAAAATCGCG	400 TAATTTGGGTAAGGTCATCGATACCCTAACGTGCGGATTCGCCGATCTCA
Figure 9	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC C/E1	PC-3-4 PC-3-8 PC-2-1 PC-2-6

79/111

401 TGGGGTATATCCCGCTCGTAGGCGCCCCATTGGGGGCGTCGCAAGGGCTCGG	D NO 451  CTCGCACACGGTGTGAGGGTCCTTGAGGGCGGTAAACTATGCAACAGG
4 E i i i i i	SEQ 1D 45 46
PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC-4-1 PC-4-6	PC-3-4 PC-3-8 PC-2-1 PC-2-6 PC-4-1 PC-4-6

- Continued 6

Figure 9

81/111

650 TATCATGTTACCAATGATTGCCCAAACTCTTCCATAGTCTATGAGGCAGA	700 TAACCTGATCCTACACGCACCTGGTTGCGTGCCTTGTGTCATGACAGGTA
PC-3-4 PC-3-8 PC-4-1 PC-4-6 PC C/E1	PC-3-4 PC-3-8 PC-4-1 PC-4-6

82/111

Figure 9 · Continued 7	701 ATGTGAGTAGATGCTGGGTCCAAATTACCCCTACACTGTCAGCCCCGAGC	751 CTCGGAGCAGTCACGGCTCCTTTCGGAGAGCCGTTGACTACCTAGCGG
Figure 9	PC-3-4 PC-3-8 PC-4-1 PC-4-6 PC C/E1	PC-3-4 PC-3-8 PC-4-1 PC-4-6 PC C/E1
	CHICATIT	ITE CHEET (DIN E 26)

Figure 9 · Continued 8	801 AGGGGCTGCCCTCTGCTCCGCGTTATACGTAGGAGACGCGTGTGGGGCA	900 CTATTCTTGGTAGGCCAAATGTTCACCTATAGGCCTCGCCAGCACGCTACG
Figure 9	PC-3-4 PC-3-8 PC-4-1 PC-4-6 PC C/E1	PC-3-4 PC-3-8 PC-4-1 PC-4-6 PC C/E1

e 9 · Continued 9	901	GIGCAGAACIGCAACTGTTCCATTTACAGTGGCCATGTTACCGGCCACGG					951	GATGGCA			
Figure 9	1	PC-5-4	PC-3-0	9-7-Jd	PC C/E1	SUE	BSTI		e PC-3-8		26)

SEQ ID NO HCV-1 HCV-3 HCV-3 HCV-3 HCC-36 HCC-38 PC1 37 197 Sa RS36 222 Sa SSEQ ID NO 12 HCC-38 SSEQ ID NO 13 SSEQ ID NO 12 SA SA SA SA SA SSEQ ID NO 12 SA SA SA SA SA SSEQ ID NO 12 SA SA SA SA SA SSEQ ID NO 12 SA SA SA SA SA SSEQ ID NO 12 12 14 15 16 17 18 18 18 18 18 18 18 18 18 18 18 18 18		3856 ACCACTGGCAGCCCCATCACGTACTCCACCTACGGGGGTTGCGGG	3991  CAAGTTCCTTGCCGACGGCGGTGCTCGGGGGCGCTTATGACATAATAA	3941  TTTGTGACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATCGGC -ATAA-TCT-GTATC-CA -AC-TATGGTCT-TCATC-CA -AC
Exagure 10  SEQ ID  HCV-1  HCV-3  HC-36  HC-38  PCI 48  BR36  HCV-1  HCV-1  HCV-1  HCV-1  HCV-1  HCV-3  HCV-1		11	12 12 22 23 33 33	11a 12a 12b 53a 3a
	Figure 10	SEQ ID 197 199 222	SSE HCV-1  SSE HCV-1  HCV-1  HC-J6  HC-J8  HC-J8  HC-J8  HC-J8  HC-J8  HC-J8  HC-J8  HC-J8	HCV - 1 HCV - J HC - J6 HC - J8 PC1 - 3

Figure 10 - Continued 1	1a ACTGTCCTTGACCAAGCAGACTGCGGGGGGGGGAGACTGGTTGTGCTCGC 1bAGTGAC	4041  CACCGCCACCCTCCGGGCTCCTGTGCCCCCATCCCAACATCGAGG  1bGAGACACAC	4091  1a AGGTTGCTCTGTCCACCGGAGAGATCCCTTTTTACGGCAAGGCTATC  1b -AGCATTCCTAC  2aGCCGGGCAGGAGTCCTG-GGT  2bGCTGGTCA-GAGCTAT  5a -AGCC-TCAGGAGGG-TCCGACT  5a -AGCC-TCAGGAGGG-TCCGACT  3a
Figure 10	HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48 BR36	HCV-1 HCV-1 HCV-J HC-J6 HC-J8 HC-J8 HC-J8 HRS-J-37 HRS-J-48	## 755 PE 26 PE 26 PE 26 PE 27

4141 CCCCTCGAAGTAATCAAGGGGGAGACATCTCTCTTTTTTCTATTCAAAA-TG-CCAGCT-G	4191 GAAGAAGTGCGACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGTGA-G-GCCTCGG-GTAT-GCAATTGA-G-GCCTGAATTAAGC-AAC-AGCCG-GCAATTAAGC-AAC-AGCCG-GCAATTAAGC-AAC-AGCCG-GCAATTAAGC-AAC-AGCCG-GCAATTAAGC-AATCAGA
1a 1b 2a 2b 5a 5a 3a	- 12 22 32 32 32 32 33 33 34 35 35 36 37 37 37 37 37 37 37 37 37 37 37 37 37
HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48 BR36	MERCY - 1  MERCY - 1

4291 GATGTTGTCGTCGTCGTGGCAACCGATGCCCTCATGACCGCCTATATACCCCCTA	CCCD	CAGG	GDLDLDLDDDDDDD-		1		4341	CTTCGACTCGGTGATAGACTGCAATACGTGTCACCCCAGACAGA	TAC	TC	TCCCTGTTGCAT-TT	TTTCCT-CGCCTGG-	TTTCCT-CGCCTGGC-		101	TCAGCCTTGACCCTACCTTCACCATTGAGACAATCACGCTCCCCAAGAAT	T-GTC	7-7-1-GT-G		TGTCTTTAG-GAG-G-	TGTCTTT-CAG-GC	
 H	1b	2a	2b	<b>5</b> a	<b>5</b> a	3a		1a	1p	2a	2b	<b>5</b> a	<b>5</b> a	3а		1a	1b	2a.	2b	<b>5</b> a	<b>5</b> a	3a
1	HCV-J	HC-J6	HC-J8	PC1_37	PC1_48	BR36		HCV	HC\	HC-	HC-	PC1	PC1_4	BR3	RULE		HCV-J	HC-J6	HC-J8	PC1_37	$PC1_48$	BR36

Figure 10 - Continued 4	1 1a GCTGTCTCCCGCACTCGGGGCAGGACTGGCAGGGGAAGCCAGG  J	1a CATCTACAGATTTGTGGCACCGGGGGGGCCCCCTCCGGCATGTTCGAC 1bGA-TAAAGAA	4551  1a CGTCCGTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTTGGTATGAGCTC  1b -C-GGC
Figur	HCV-1 HCV-J HC-J6 HC-J8 PC1 3	SIBSTITUTE SHEET (RINE 26)	HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48

4741  GAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCTAGGGC CCC	4791  TCAAGCCCCTCCCCATCGTGGACCAGATGTGGAAGTGTTTGATTCGCCG-T-ATG-CGTCC-C-AG- CAC	4841  TCAAGCCCACCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCT -AAGTGCTCGC-TTATAGACTTCG
11 11 12 12 13 13 13		12 22 23 33 33
HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48 BR36	HCV-1 HCV-1 HC-J6 HC-J8 HC-J8 PCI 37 BR36	### TOP

# 92/111

		•
4891 GTTCAGAATGAAATCACCCTGACGCACCCAGTCACCAAATACATCATGACACCCGGTTGGGCACCCGGTTGGCCGACCGGTTGGCCGACC	4941  ATGCATGTCGGCCGACCTGGAGGTCGTCACGAGCACCTGGGTGCTCGTTG	4991  GCGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTGTCAACAGGCTGCGTG ATGCCAGGCC
1a 1b 2a 2b 5a 3a	118 128 128 138 388 388 388	12 12 12 13 13 13 13
HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48	HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48 BR36	HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48

.

.

Figure 10 - Continued 8	5041	GTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA		2a TGCA-CC-CT-GCA-G-TAA-CA-CGAG-C-TCG-TGCG-			CCTAC-CTATC	GTTCATAAGCGGGCG-	5091	O	ı	AGTGAG-CTT	1	TGAT-AAGC-AT	TG-CAT-AAGC-AT	-AAGGT-GT-A-C-A-A		ACCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCA	ı	ש	ľ	ט	CGGCTGCG-GACACGTGCCA-TGAA	CTGCCATACTCA-G-AA-ATC-C
Figure		- 1	HCV-J	HC-J6	38	PC1_37	$PC1_48$	BR36	SUB	HCV-	HCV-	HC-J6	HC-J	PC1_	$PC1_4$	E 20	5)	HCV-1	HCV-J	HC-J6	HC-78	PC1_37		BR36

6 panu	5191 AAGGCCCTCGGCCTCCTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCGAT-GCAATAAAATC-A-AC-ACAAT-AAT-ATAATAAAATC-A-AC-ACAATA-AA	5241  CCCTGCTGTCCAGACCAACTGGCAAAACTCGAGACCTTCTGGGCGAAGC  TC-TGGG-TA-  ACGG-TTCTCCGG-ACAA-  GAA-AT-ATCACCGG-TC-A-  GAA-C-AC-T-TGTGA-CGGCTCAG	5291 AT -C -C -C -C -C -C -C -C
- Conti	18 19 19 19 19 19 19 19 19 19 19 19 19 19	11a 12a 23a 3a 3a	110 110 22 52 53 33
Figure 10 - Contin	HCV-1 HCV-J HC-J6 HC-J8 PC1_37 PC1_48 BR36	ATAN HERV-1 HCV-1 HC-J6 HC-J8 PC1 37 BR36 48	, (92 HCV-1 HCV-J HC-J6 HC-J8 PC1 37 PC1 48 BR36

9	5/	1	1	1

SEQ ID NO	2.00	<b>⊄</b> ;;;;
1286 TTGSPITYSTYGKFLA	G	LATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKODELA
HCV-1	HCV-J HC-J6 HC-J8 PC-1-48	HELD HELD HELD HELD HELD HELD HELD HELD

-¥.

1586 LVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEITLTHPVTKYI 	1646 MTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRVVLSGKPAIIPDREVLYREF -A	1706 DEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLETFWAKHASRAALE-QRIML-S-IQQP-QASSRAALE-QRMML-S-IQQP-QI-SS-P-V-QASKAALE-QRMML-S-IQQ-TQD-QI-SS-PQASKAALE-QRMML-S-IQQ-TQD-QI-SS-PQASKAALE-QRMML-S-IQ
HCV-1 HCV-J HC-J6 HC-J8	HCV-1 HCV-J HCV-J HC-J6 HC-J8 HC-J8 HC-1-48	HCV-1 HCV-J HC-J6 HC-J8 PC-1-4

98/111

330 340 350 350 370	LTMIL-YAA-V-ELV-EI-F-GVF-LQ-AIAI -AVGM-V-HVLTLF-IMIYQAIIMVM IGISH-M-LTLF-LVS-TMLQVIIM LVVVI-ISFAAYAS-ATVLF-	380
360 		410 AKQNVQL IN PS-KIV -R-KI PQ-KLV PS-KLV
350    AGAHWGVLA  V	-F-GVF MI VS-TM-	400 SGFVSLLAPG ASL-W-SQ- RTLTGMFSL- AAG-FTT- AA-AG-FDI- RLTDIFST-
340 	-V-ELV-EI  -LTLF-II  -LTLF-L  VVI-I	390 TGGSAGHTVS RVASSTG VTA-NAR S-QERA T-SRHTG -AMAQSIY SSAQ-TY
330   	LTMIL-YAA -AVGM-V-HV- IGISH-M	380 400 410 *    E2
1a 1b	2b 3a 3b 5a	1a 2b 3b 3b 5a
HCV1 HCVJ HCJ6	HCJ8 NZL1 HCVTR BE95	HCV1 HCVJ HCJ6 HCJ8 NZL1 HCVTR

99/111

	* NW '	، ياي
	111 111	520
	0 460   CPERLASCRPLTDFD MSAIDE-A SG-DR QSK-I-F-R	510 / //YCFTPSPW
	45 NSSG -A	480 490 500 510 520   Comparison of the comparis
	30 440 DSLNTGWLAGLFYHHKFQFI-AA-RHFST-SQFIY	480 490 500  GSGP/DQRPYCWHYPPKPCGIVPAKSVCG PESS/SQ VTN-E-M
nued 1	430 	480 GSGP/DQRPYCWHY PESS/ VTNDG-M ITS-D
2 - Continued 1	1a 2b 3a 3b 5a	1a 1b 2b 3a 3b 5a
Figure 12	HCV1 HCVJ HCJ8 HCJ8 NZL1 HCVTR	HCV1 HCVJ HCJ6 HCJ8 NZL1 HCVTR BE95

100/111

ned 2	530 540	TYSWGENDTDVFVLNNTRPPL	ELLTRP-QG		TER			I
Figure 12 · Continued 2		<u>Ja</u>	<b>1</b> b	2a	<b>5</b> p	3a	3b	5a
Figure 12		HCV1	HCVJ	HCJ6	нслв	NZL1	HCVTR :	BE95

	980 CCCTACGACGGCGTTGGTAATGGCTCAGCTGCTCCGGATCCCAAAAAAA	つつりせつひつつ TOO TOO TOO TOO TOO TOO TOO TOO TOO T		-AAGG-AT-GA-	CAACC-AGGT-GT-	AACC-AGGT-GT-	ACC-A	CC-A	-ACC-AGGT-GT-	AATC-A-	CA-	AAA-	-ACC-AGG-AT-G	-CC-CGI-GI-	-GCG-TA-CAA-CCGT-CGC-A-GCGCG-G-T-	BDLG-CGCLIG-L-CG	G-CA-CAA-CCGT-CGC-A-GCGCG-	TA-CAA-CC-CCT-TGCCGCTTG-T-TG-C	GTAGGGGG	GTAGGGCG-CGT	GG-AGTG-CGTT-GC-	GTAGGGG-TGT-G-	C-GGCT-AGTC
c	ır 1a	1a	1a	1p	1b	1p	1p	1p	1p	1p	1p	1p	1b	11	2a	Sp	2a	<b>5</b> p.	3a	3a	3a	3а	5a
	ב אם ב																						157
Figure 13	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91					옆 HCV-JK1	HCUNK	N- NCN-N	HC-J6			HC-J7	NZL1	HEM26	TH85	US114	BE95

- Continued 1	1030 1a ATCTTGGACATGATCGCTGGTGCTCACTGGGAAGTCGCAATAACA	A		1b GGG-G-G-G-C		99-9B	99-999	GGTB	GTG-G-G-G-GGGG	GAG-G-TGGC	GGTG	8L-9-999	GGG-GA-A	GA-CG-GGGC	A-ACT-GC	GC-CATTTTCC-GCTTG	A-ACTAGCGCATTCC-	GC-TGG-TGTTCC-GCT	T-GCAGCGCTCAT	T-GCACGCTCATC-	T-GCAACGCT	T-GCTAG-ACGCT	
Figure 13 - Con	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91			HCV-CHINA		S HCV-JK1	HCUNK		HC-J6			HC-J7	NZL1	HEM26	TH85	US114	BE95

Figure 13 - Continued

1080	GTATTTCTCCATGGTGGGGAACTGGGGGGGGTCCTGGTAGTGCTGCTGC			CC-ATA-T	CC-AT	CC-ATATAGC	CC-AT	CC-ATA-TA-TTA-TA-T-	CC-ATA-TA-TA-T-	CC-ATGA-TTTTTA-TA	CC-ATA	CC-ATA	CC-ATT-AA-T-C-A	CC-ATCTTTA-T-	CCTCAAGCGAAG-TCA-TTT	C	CCTCAAGCG	C	CA	CACACTCGCTA-CA-CGG-	CACAACCGCTA-CAG-	CACAC	AC-ATG-ATCCTA-CGC-GC
	la '	Ia	1a	1p	1b	1p	1p	$^{1p}$	1p	1p	1p	1p	1p	$^{1p}$	2a	<b>2</b> p	2a	<b>3</b> p	3a	3a	3a	3a	<b>5</b> a
	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91	S HCV-JTA	HCV-JTB	HCV-CHINA	M HCV-T	S HCV-JK1	HCUNK	HCV-N	IN HC-J6	HC-78	(9) HC-JS	HC-J7	NZL1	HEM26	TH85	US114	BE95

1130	TATITIGCCGGCGTCGACGCGGAAACCCACGTCACGTCAC	OSSO SE LA CARROLLA C	-GAA				-ACGT-G	TT ACG TT		'TCGT-T-			I-VI	T-ACAG	TAC-GTTTTC->	-GTAACCT-TTCG-	3TA-CG-AC-GTT-C	ATC	AGTCC-CAT-TACT	TV::::::::::::::::::::::::::::::::::::		/ - プエン L	-GAGTTACTGA-TT-GC-CTCCAG-
	la	1a	1a	1b	1b	1p	1p	1p	1p	1b	1p	1b	1p	1b	2a	<b>2</b> p	2a	2b	3a	3а	3a	3a	Sа
	HCV-1	нсн-н	HC-J1	HCV-J	HCV-BK	HC-J4.83	2 HC-J4.91	SE HCV-JTA	HCV-JTB	HCV-CHINA	S HCV-T	HCV-JK1	J HCUNK	JUSH HCV-N	HC-76	<b>ම</b> HC-J8	HC-J5	HC-J7	NZL1	HEM26	TH85	US114	BE95

1180	CACACTGTGTCTGGATTTGTTAGCCTCCTCGCACCAGGCGCCAAGCAGAA	-GCAC-GGCG-TTA	-G-G-CA	I I	A-ACACCAACA-GC-CGTC-A-GTAGTGC-GTCT	CACCCACGC-C-CGTCTTGGTCTG	GGTCT	-G-CACACCCAGA-CG-CACGTC-TTA-C-AGC-GGCCG	-G-CACACCCAGGG-C-CGTC-TTA-CGC-GGCC	-G-T-CACCCTCGCACGTCT-TATGTCT	-GCACCCACA-TC-C-CGTCTT-TAAGGTCC	GCACCCGCC-CGCGTC-TTAGTTT-GGCT	-GGG-C-CTAGCTCGC-AACGTCT-TAGC-TGC-GGTTC-	- 1	T-AC-CCAGGACCC-CACCGA-GTT-C-TTTG	-GTCCG-GGC-C-GT-TA-TA-T-TT	GCACACCAGGCCACCA-GTT-CT-TT-G	TCTAGAG-C-CCATAGCTTCGG-	-GTCA-ACCCAA-CGC-G-TTT-T-ACATCC-A	TGACCAGAGA-A-CTTT-TA-TGTGCGC	TGAC-ACA-GCTTAAT-GGCGAA	-GTGAC-ACA-GCAC-GT-TTC-GGCGT	AGACACA-C-CCTCAT-TAA-C-GCGC
	1a	la	la	1p	1b	1b	1b	1b	1b	1b	1b	1 <b>b</b>	1p	1b	2a	<b>2</b> p	2a	<b>2</b> p	3a	3a	3a	3a	<b>5</b> a
	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83			-				•		HC-J6			HC-J7	NZL1	HEM26	TH85	US114	BE95

c paniri	1230 CGTCCAGCTGATCAACAACAACAACAATTGGCAACAAAAAAAA	-AA		AG-G	-)W	-)V		-) V	>	)	TDD	9DV	TDWLJ	D0VV	-D	アープン・マー	D	7-704-4		BULL		CC	A
2000	1a	la	1a	1b	1b	1b	1b	1b	1b	1p	1p	1b	1b	1b	2a	Sp	2a	Sp	3a	3a	3a	3a	<b>5</b> a
	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91	s HCV-JIA	HCV-JTB	HCV-CHINA	ा HCV-T	S HCV-JK1	HCUNK	HCV-N	HC-J6	F HC-78	(9) HC-J5	HC-J7	NZL1	HEM26	TH85	US114	BE95

\_1

•

;

.

#1

1280	TGAACTGCAATGATAGCCTCAACACGGCTTGGTTTGGTT	TAIDIII TOOOOOTTOOTOOTOOTOOOOOTTOOOOOTTOOOOOTTOOOO								・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・・							TO TO THE PROPERTY OF THE POST			T9-TU-W-W-D	TW-TTTW-W-DD	C-A-A	-778-TCA-A87
	la	1a	1a	1b	1p	1p	1p	1p	1p	$^{1}$ p	1b	1p	1p	1b	2a	<b>2</b> p	2a	Sp	3a	3a	3а	3a	Ба
	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91					•		HCV-N				HC-J7	NZL1	HEM26	TH85	. US114	BE95

	GCCA	1	!	-AT-	TG	A-TG	A-TG	AG	AG	A-TG	A-TG	TG	A-TG	TG	-GAG-A	AA	CGAG-AT-	-GAGA	E i	- L	-AA-	 	] ; ;
	3GGCCCTATCAGTTAT			TCC-C	TCI-C		DDD	DDD	DD	C	DDI	LCCCC	DDDI		G-CT-ACAAGA	AA-CT-GGAACGAAA	A-CT-GCAACGA	AA-CT-GGAAGA	CT-A-CAG	T-CT-G-CAG	CT-G-CAG	T-CT-G-CAG	AAC
1380	ACCCCTTACCGATTTTGACCAGGGCTGGGGCCCCTATCAGTTAT	·		CA-CGATGC-CTG	CAAGA-A-GCA	CAGA-TGGC-CA	CAGAGGC-CA	CTA-CGA-A-GC-CTA	CTAGA-A-GC-CTA	CAGATACACT	TTAGA-A-GCTA	TAGA-AGGC-CTAG	CAGATACAC-CGG	CTAGA-A-GCA	CAGTA-CGAG-CCCGGGTA	CGGGGGACG-ATC	CAG-A-CGAG-CCCGGATAG	TAAGGGATCG-ATCG	GA-CTTTCCAGGA	GA-CTTCCCAGGG	GA-CTCCCA-TG	GA-CTTCCCAGGG	GGGAC
	la	1a	1a	1p	1b	1b	1p	1b	1p	$^{1}\mathrm{p}$	1p	<b>1</b> p	$^{1}$ p	$^{1}$ p	2a	<b>2</b> p	2a	<b>2</b> p	3a	3a	3a	3a	5a
	HCV-1	HCH-H	HC-J1	HCV-J	HCV-BK	HC-J4.83	HC-J4.91	HCV-JTA	HCV-JTB	HCV-CHINA	HCV-T	HCV-JK1	HCUNK	HCV-N	HC-J6	HC-J8	HC-J5	HC-J7	NZL1	HEM26	TH85	US114	BE95

	GGCACTACCCCCA		t 1 1 1 1 1	T9-9	TA	I9-9L	TG-GT	TT	TT	1	C-BC	-B	1 1 1 1 1	G	A	9	A		T	T			L
	GACCAGCCCCTACTGCTGGCACTACCCCCCA	G-A	ATT-	E I	A-GAT	TA-GTT	TA-GTT	TA-GT	TA-GT	A-GTT	T	AA-GT	TA-GT	A-GTT	TAT-A-A-	AT-A-G-	TAT-A-A-	AT-A-A-	'TG-CA-A	AG-CAAAG	TG-CAAA	TG-CAAAG	TG-CAAAAT
1430	ACGGAAGCGGCCCC	- I	8	TGCCTGAGAT-G	-GTCTA-AT-A	-GCCTGA-AG	-GCCT-A-AG	-GCCTG-ATG	-GCCTG-G-A-TTG	-GCCTGATAT-G	-G-CTGA-ATAG	-GTCTCAT-G	-GCCTCAT-ATTTG	-TCCT-AA-AG	-T-TC-C-AATAGAG	TC-C-AA-GATGGG	-T-TC-C-AATAGAA	-T-TT-C-AA-GAGGAG	ATC-CTTTCT	ATCTCTT-GTCC	ATC-CTTCT	ATC-CATT-TTCT	AT-TCGTAGT
	1a	1a	1a	1p	1b	1b	$^{1}$ p	1b	1b	1b	1b	1b	1b	1b	2a	2p	2a	5p	3а	3a	3a	3a	<b>5a</b>
	HCV-1	нсн-н	HC-J1	HCV-J	HCV-BK	HC-J4.83	_			HCV-CHINA			HCUNK	HCV-N	HC-J6	HC-J8	HC-J5	HC-J7	NZL1	HEM26	TH85	US114	BE95

Continued 10	1480  AAACCTTGCGGTATTGTGCCCGCGAAGAGTGTG -GTCACA  CGGGCTTC-CAG  CGGTCATTC-CAG  CGGTCATTC-CAG  CGGTCATTC-CAG  CG-AGTCATTC-CAG  CG-AG-TCATTC-CAG  CG-AG-TCATC  CG-AG-TCATT-CAG  CG-TCATT-CAG  CG-TCATT-CAG  CG-TCCCCC  GGC	
- Cont	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
Figure 13	HCV-1 HCY-1 HCY-1 HCY-31 HCY-31 HCY-BK HCY-BK HCY-74.83 HCY-74.91 HCY-74.91 HCY-74.91 HCY-74.91 HCY-74.91 HCY-74.91 HCY-74.93 HCY-74.91 HCY-74.93 HCY-74.93 HCY-74.91 HCY-75 HCY-76 HCY-76 HCY-76 HCY-76 HCY-76 HCY-77 NZL1 HEM26 TH85	



# WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5:		(11) International Publication Number	r: WO 94/25601
 C12N 15/51, C12Q 1/68, 1/70, A61K 39/29 G01N 33/576, C07K 7/04	A3	(43) International Publication Date:	10 November 1994 (10.11.94)

(21) International Application Number: PCT/EP94/01323

(22) International Filing Date: 27 April 1994 (27.04.94)

(30) Priority Data:
93401099.2 27 April 1993 (27.04.93) EP
(34) Countries for which the regional or
international application was filed: GB et al.

international application was filed: GB et al.
93402019.9 5 August 1993 (05.08.93) EP

(34) Countries for which the regional or international application was filed: GB et al.

(71) Applicant (for all designated States except US): N.V. INNO-GENETICS S.A. [BE/BE]; Industriepark, Zwihnaarde 7, Box 4, B-9052 Ghent (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MAERTENS, Geert [BE/BE]; Zilversparrenstrasse 64, B-8310 Brugge (BE). STUYVER, Lieven [BE/BE]; Hoogstraat 27, B-9340 Lede (BE).

(74) Agent: GROSSET-FOURNIER, Chantal; Grosset-Fournier & Demachy S.A.R.L., 103, rue La Fayette, F-75010 Paris (FR). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published** 

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 02 March 1995 (02.03.95)

(54) Title: NEW SEQUENCES OF HEPATITIS C VIRUS GENOTYPES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC AGENTS

### (57) Abstract

The present invention relates to a polynucleic acid composition comprising or consisting of at least one polynucleic acid containing 8 or more contiguous nucleotides corresponding to a nucleotide sequence from the region spanning positions 417 to 957 of the Core/E1 region of HCV type 3; and/or the region spanning positions 4664 to 4730 of the NS3 region of HCV type 3; and/or the region spanning positions 4892 to 5292 of the NS3/4 region of HCV type 3; and/or the region spanning positions 8 023 to 8 235 of the NS5 region of the BR36 subgroup of HCV type 3a; and/or the coding region of HCV type 4a starting at nucleotide 379 in the core region; and/or the coding region of HCV type 5, with said nucleotide numbering being with respect to the numbering of HCV nucleic acids as shown in Table 1, and with said polynucleic acids containing at least one nucleotide difference with known HCV type 1, and/or HCV type 2 genomes in the above-indicated regions, or the complement thereof.

### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

Austria	GB	United Kingdom	MR	Mauritania
Australia	GE	Georgia	MW	Malawi
Barbados	GN	Guinea	NE	Niger
Belgium	GR	Greece		Netherlands
Burkina Faso	ผม			Norway
Bulgaria	IR			New Zealand
Benin				Poland
Brazil				Portugal
				Romania
				Russian Federation
				Sudan
				Sweden
	KR			Slovenia
				Slovakia
, = <del>-</del>				
				Senegal Chad
				Togo
		<del></del>		Tajikistan
				Trinidad and Tobago
				Ukraine
				United States of America
				Uzbekistan
riance -	MIN	MANPOILE	VN	Vict Nam
	Australia Barbados Belgium Burkina Faso Bulgaria Benin	Australia GB Barbados GN Bolgium GR Burkina Faso HU Butgaria IE Benin IT Brazil JP Belarus KE Canada KG Central African Republic KP Congo Switzerland KR Côte d'Ivoire KZ Cameroon LI China LK Czechoslovakia LU Czech Republic LV Germany MC Denmark MD Spain MG Finland ML	Australia  Barbados  GN Guinea  Bolgium  GR Greece  Burkina Faso  HU Hungary  Bulgaria  Benin  IT Italy  Brazil  Benarus  Canada  Central African Republic  Congo  Switzerland  Côte d'Ivoire  KE KZ  Cameroon  China  China  Czech Republic  Czech Republic	Australia GE Georgia MW Barbados GN Guinea NE Bolgium GR Greece NL Burkina Faso HU Hungary NO Bulgaria IE Ireland NZ Benin IT Italy PL Brazil JP Japan PT Belarus KE Kenya RO Canada KG Kyrgystan RU Central African Republic KP Democratic People's Republic SD of Korea SE Switzerland KR Republic of Korea SI Côte d'Ivoire KZ Kazakhstan SK Cameroon LI Llechtenstein SN China LK Sri Lanka TD Czechoslovakia LU Luxembourg TG Czech Republic LV Latvia TJ Germany MC Monaco TT Denmark MD Republic of Moldova UA Spain MG Madagascar US Finland ML Mali UZ

### INTERNATIONAL SEARCH REPORT

nal Application No PCT/EP 94/01323 A. CLASSIFICATION OF SUBJECT MATTER IPC 5 C12N15/51 C12Q1/68 C12Q1/70 A61K39/29 G01N33/576 C07K7/04 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 5 C12N C12Q C07K A61K G01N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X J. GEN. VIROL., 1,2, vol.73, 1992 6-11, pages 1131 - 1141 S.W.CHAN ET AL. 'Analysis of a new hepatitis C type and its phylogenetic relationship to existing variants' cited in the application see figures 3,5 X BIOCHEM. BIOPHYS. RES. COMMUN., 1,2,6-8, vol.183, no.1, 1992 pages 334 - 342 S. MORI ET AL- 'A new type of hepatitis C in patients in Thailand cited in the application see figure 1 see the whole document -/-l XI Further documents are listed in the continuation of box C. lx l Patent family members are listed in annex. Special categories of cited documents: T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the 'A' document defining the general state of the art which is not considered to be of particular relevance E. earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docudocument referring to an oral disclosure, use, exhibition or Other means ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 14 October 1994 **D 1** -02- 1995

J

Name and mailing address of the ISA

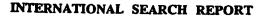
Authorized officer

SKELLY J.M.

## INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/01323

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
tegory "	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
\	PROC. NATL. ACAD. SCI. USA, vol.89, 1992 pages 7144 - 7148 T. A. CHA ET AL 'At least five related but distinct genotypes of hepatitis C virus exist' cited in the application see figure 1	1
(	WO,A,92 19743 (CHIRON CORPORATION) 12 November 1992 cited in the application see figure 2	1,2, 6-11, 15-23
A	WO,A,93 06126 (CHIRON CORPORATION) 1 April 1993 see the whole document	9-11
X	VIROLOGY, vol.180, 1991 pages 842 - 848 A.WEINER ET AL. 'Variable and hypervariable regions are found in the regions of HCV corresponding to the flavivirus envelope and NS1 proteins' see figures 1,2	1,2, 6-11, 15-23
<b>X</b>	J. GASTROENTEROL. HEPATOL., vol.8, 1993 pages 150 - 156 K. CHAYAMA ET AL. 'Genotypic subtyping of hepatitis C virus' see the whole document	1,2,6-8, 22
K,P	WO,A,93 10239 (COMMON SERVICES AGENCY) 27 May 1993 see the whole document	1,2, 6-11, 15-23
(,P	BIOCHEM. BIOPHYS. RES. COMMUN., vol.192, no.2, 1993 pages 635 - 641 L. STUYVER AT AL. 'Analysis of the putative El envelope and NS4a epitope regions of HCV type 3' see the whole document	1,2,6-8, 22
(,P	J. GEN. VIROL., vol.74, 1993 pages 1093 - 1102 L. STUYVER ET AL. 'Typing of hepatitis C virus isolates and characterisation of new subtypes using a line probe assay' see the whole document	1,2,6-8, 22
	<del>-/</del>	



Inter vial Application No
PCT/EP 94/01323

		PCT/EP 94/01323				
C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT						
ategory *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.				
( <b>,</b> P	J. CLIN. MICRO., vol.31, no.6, 1993 pages 1493 - 1503 P. SIMMONDS ET AL. 'Mapping of serotype-specific immunodominant epitopes in the NS4 region of hepatitis C virus' see the whole document	1,2, 6-11, 15-23				
	·					
	•					
	•					
	•					
	•					
		-				
1						

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

### INTERNATIONAL SEARCH REPORT

ir	ational application No.				
•					
207	/PD 04 / 01000				

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This inte	rnational search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
ı. 🗌	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	.  Claims Nos.:  because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	rnational Searching Authority found multiple inventions in this international application, as follows:
	See annex.
ı. 🗌	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. 🗌	As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
	As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
_	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  1,2,6-10 partially; 11,15-23 partially.
Remark (	The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

#### РСТЛЅА/210 FURTHER INFORMATION CONTINUED FROM

### LACK OF UNITY OF INVENTION

1;2;6-10 (partially); 11;15-23 (partially): 1. Claims:

Polynucleotides or amino acids corresponding to the core/El region of HCV subtype 3a and

their uses.

1;2;6-10 (partially); 11;15-23 (partially): 2. Claims:

Polynucleotides or amino acids corresponding

to other regions of the genome of HCV subtypes 3,

3a and 3c and their uses.

1;3;6-10 (partially); 13;15-23 (partially): 3. Claims:

Polynucleotides or amino acids corresponding

to various regions of the genome of HCV subtype 5

and their uses.

1;4;6-10 (partially); 12;15-23 (partially): 4. Claims:

Polynucleotides or amino acids corresponding to various regions of the genome of HCV subtype 4 and .

their uses.

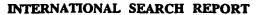
1;5;6-10 (partially); 14;15-23 (partially): 5. Claims:

Polynucleotides or amino acids corresponding to

various regions of the genome of HCV subtype 2d

and their uses.





information on patent family members

Inter mail Application No PCT/EP 94/01323

Patent document cited in search report	Publication Patent family date member(s)			Publication date
WO-A-9219743	12-11-92	AU-A- CZ-A- EP-A- JP-T-	2155892 9302377 0585398 6508026	21-12-92 13-04-94 09-03-94 14-09-94
 WO-A-9306126	01-04-93	NO-A- AU-A- CA-A- EP-A- FI-A-	934019 2643692 2116764 0608261 941199	05-11-93 
WO-A-9310239	27-05-93	AU-A- CA-A- EP-A- FI-A-	3088792 2123875 0610436 942369	15-06-93 27-05-93 17-08-94 19-07-94